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"Sleep on it", but how?

-

Targeted Memory Reactivation During Sleep To Enhance Relational Memory And Cognitive Flexibility

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Thesis summary

While a third of life is spent asleep, it is reasonable to admit that the exact reasons remain unclear. However, decades of intense research in the fields of cognition, biology, and psychology have brought strong evidence about the relationship between spontaneous reactivations during sleep of active encoding neuron networks and the emergence of abilities to develop original, innovative, and adaptive strategies. On that basis, a convincing technique called targeted memory reactivation (TMR) that aims to mimic spontaneous replay of memory has emerged.

The present thesis combined TMR during slow-wave sleep (SWS) and rapid-eye movement (REM) sleep with an electrophysiological approach to examine behavioral benefits over time and the dynamics of neural correlates susceptible to explain them.

Overall, chapter 2 has provided convincing evidence about the benefits of a full night of sleep in the consolidation of memory and the emergence of transitive inference (TI) abilities after a full night of sleep and after a week. Chapter 3 shed light on the impact of TMR during REM sleep in the progressive increase of TI accuracy through a week, the existence of theta/gamma coupling as a potential neural correlate of TI abilities, and finally. Lastly, chapter 4 provided convincing and encouraging findings about the role of TMR during SWS in the immediate improvement of TI ability and its maintenance over time, and the role of delta/sigma and delta/gamma coupling in the formation of associations between premises to create inferences.

Taken together, these findings provided insightful evidence about the crucial role of sleep and the powerful potential of TMR in the formation of relational memory and long-term memory consolidation, but also pointed out the numerous remaining gaps and open questions about the neural correlates and their interaction in the formation of long-term cognitive flexibility.

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Contributors

Chapter 3 and 4:

The manual sleep scoring was performed with PSG Score interface, a MATLAB toolbox designed by Miguel Navarrete.

Chapter 4:

The script used to detect slow oscillations and deliver cueing sound when applying TMR was designed by Lorena Santamaria.

Jay Lord, Megan Wadon and Caterina Leitner have participated as second experimenters during overnights and provided assistance during the wire-up before sleep.

List of abbreviations

ACh = Acetylcholine

Adj. R^2 = Adjusted R^2

AIC = Akaike Information Criteria

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

ASC = Active system consolidation

BDNF = Brain-Derived Neurotrophic Factor

BiOtA = Broader form of the information overlap to abstract

CI = Confidence interval

CL-TMR = closed-loop TMR

EEG = Electroencephalogram

EMG = Electromyography

EOG = Electrooculography

ER = Evolution rate

ERDS = Event-related desynchronization/synchronization

ERPs = Event-Related Potentials

fMRI = Functional magnetic resonance imaging

HAD a = Hospital anxiety and depression (anxiety)

HAD d = Hospital anxiety and depression (depression)

iEEG = intracranial EEG

iOTA = Information overlap to abstract

ISI = Index of Severity Insomnia

KSS = Karolinska sleep scale

LAMF = Low-amplitude mixed-frequency

LTD = Long-term depression

LTP = Long-term potentiation

MCH = melanin-concentrating hormone

MDA = Mean Decrease Accuracy

MFDFA= multifractal detrended fluctuation analysis

MI = Modulation index

MMT = Multiple memory trace

mPFC = medial prefrontal cortex

NMDA = N-methyl-d-aspartate

nREM = Non-rapid eye movement

ns = Non-significant

OLS = ordinary least squares

OR = Odd ratio

PAC = phase-amplitude coupling

PET = positron emission tomography

PGO = Ponto-geniclo occipital

REM = Rapid eye movement

RLPFC = rostrolateral prefrontal cortex

ROIs= Regions of interest

RSA = representational similarity analysis

RSA (chapter 4 only) = rhythmic slow oscillations

SHY = Synaptic homeostasis hypothesis

SO = Slow-oscillation

SRTT = Serial Reaction Time Task

SWS = Slow-wave sleep

TI = Transitive inference

TMR = Targeted memory reactivation

vmPFC = ventromedial prefrontal cortex

YASA = Yet Another Spindle Algorithm

Chapter 1: GENERAL INTRODUCTION

1 - Preface

Sleep can be defined as "a rapidly reversible state of immobility and greatly reduced sensory responsiveness" (Siegel, 2008, p. 208). Moreover, sleep is homeostatically regulated, meaning that a reduction in sleep is subsequently followed by an increased need for sleep ('sleep rebound'). Although sleep appears to be fundamental for many species, many questions remain about its function. Historically, sleep has been seen as a passive state, a state of mere inactivity, but starting with the first electroencephalographic (EEG) recording of sleep in 1924, this has slowly changed (Haba-Rubio & Krieger, 2012). For the first time, sleep could be measured and studied objectively, and recordings of full nights of sleep thereafter revealed that the brain appears to be quite busy while asleep. Sleep is characterized by different stages and oscillatory patterns, and it is quite possible that each of these patterns serves different or complementary functions.

Sleep is the opposite state of wakefulness and is characterized by a temporary loss of consciousness of the external world, but without a loss of sensory sensitivity, as is the case in a coma. Concretely, sleep can be defined as "a rapidly reversible state of immobility and greatly reduced sensory responsiveness" (Siegel, 2008, p. 208). In simple terms, sleep can be characterized by two specific stages: predominant slow-wave sleep (SWS) in the first part of the night and predominant REM sleep (Rapid Eye Movement) in the later part of the night. During slow-wave sleep, the body and brain are at rest, and muscle tone decreases. It's also during this phase that growth hormone, also known as somatotropin, is synthesized. On the other hand, REM sleep is more conducive to regulating homeostatic functions and is characterized by intense brain activity that sharply contrasts with a near-complete loss of muscle tone. This stage is also a privileged period for dreams with high emotional valence.

Not only recognized for its restorative properties, sleep soon appeared to be strongly associated with memory. Indeed, from an initial passive and protective state against external interference (Jenkins and Dallenbach, 1924), sleep rapidly became the

cornerstone of memory consolidation (Diekelmann and Born, 2010; Rasch and Born, 2013). More recently, sleep research went further, suggesting that sleep would be crucial not only for the consolidation process of memory but also for its reorganization and transformation (Lewis and Durrant, 2011; Lewis et al., 2018).

Among the multiple physiological and biological mechanisms proposed to explain sleep-related benefits on memory transformation, "replay" became rapidly considered the core process of progressive memory integration (Wilson and McNaughton, 1994; Maquet et al., 2000; Peigneux et al., 2004). On that basis, a recent and promising technique, now widely used, emerged in order to promote neural replay and thus improve memory integration (Rasch et al., 2007; Rudoy et al., 2008). The so-called "targeted memory reactivation" protocol, which consists of pairing cues with specific material to learn and then re-presenting the cues during sleep to promote memory reactivation and improve behavioral abilities (Tamminen et al., 2017; Goldi and Rasch, 2019), has proven efficiency in numerous applications like memory consolidation (Fuentemilla et al., 2013; Sterpenich et al., 2014; Cairney et al., 2018; Goldi et al., 2019), grammatical generalization (Batterink and Paller, 2017), language acquisition (Batterink et al., 2017; Schönauer et al., 2018), classical music (Gao et al., 2020), procedural (Cousins et al., 2014; Rakowska et al., 2021), and emotional memories (Cairney et al., 2014; Pereira et al., 2023). However, neither the mechanisms behind TMR-related benefits nor their duration and evolution over time are clear.

The overall objective of the present thesis is to further knowledge about the role of sleep and, to a greater extent, TMR in memory integration and restructuring to promote transitive inference ability, a specific type of relational memory. For that purpose, three experimental behavioral tasks, comprising brain recording and TMR application during SWS and REM sleep, will be performed. After a general introduction that aims to provide relevant background about the evolution of the perception of sleep and memory over time, the present thesis will focus on the sleep and TMR-related behavioral benefits in the short and long term. Finally, this thesis will aim to investigate the neural correlates susceptible to explain these benefits.

2 - Physiological aspects of sleep

After the first electroencephalogram (EEG) recorded in humans in 1924 by Hans Berger, which revealed the presence of brain waves later called "alpha" and "beta" (Berger, 1929), the perception of the sleep state as a simple "resting mode" changed. Subsequent decades of research have furthered knowledge about sleeping brain activity and the complexity behind it. Indeed, it is now well known that sleep is characterized by specific brain-wave patterns, variations of muscle activities (recorded by electromyography - EMG), and eye movements (recorded by electrooculography - EOG) (**Figure 2**). Ideally, a full night of sleep is divided into 5 or 6 cycles of 90 minutes each. Each cycle comprises two main stages, namely non-rapid eye movement (nREM) and rapid eye movement (REM). nREM sleep can be subdivided into four groups, called N1, N2, slow-wave sleep (SWS) or N3, and REM sleep or R (Iber et al., 2007) (**Figure 1**). nREM is predominant during the early part of the night, whereas REM sleep duration tends to increase as the night progresses (Patel et al., 2022).

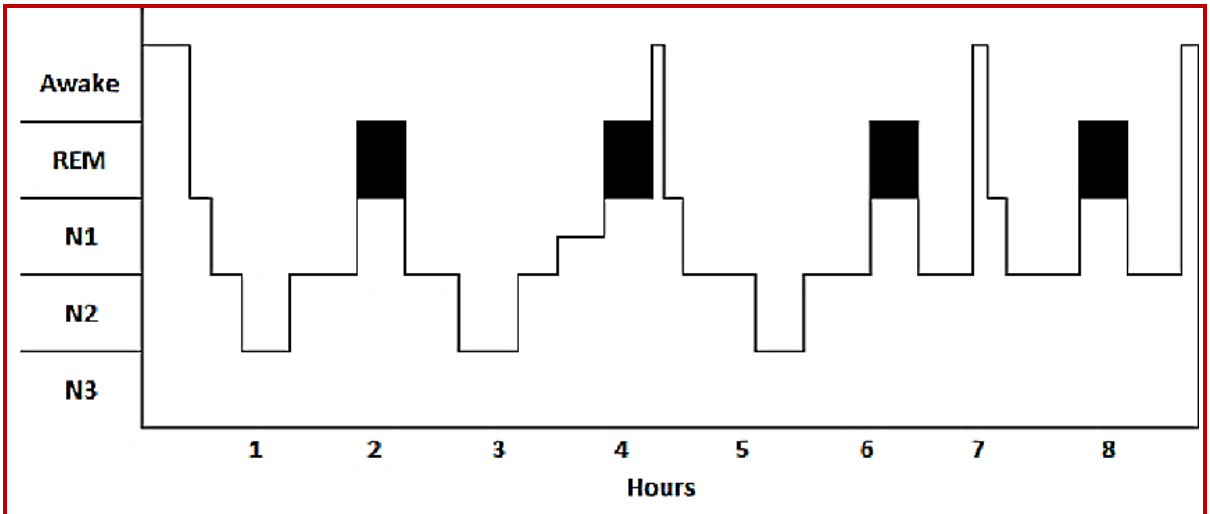


Figure 1. Hypnogram representing a theorical night of sleep.
Source: from Miller, Christopher & Kyle, Simon & Melehan, Kerri & Bartlett, Delwyn. (2015). Chapter 4. Methodology for the Assessment of Sleep

Stage N1 constitutes around 5% of total sleep duration. It is mainly represented by theta rhythm oscillations (4-8 Hz). N1 is the lightest sleep stage, beginning when more than 50% of the alpha waves (8-12 Hz) that characterize the wake stage with eyes closed are replaced with low-amplitude mixed-frequency (LAMF) activity (Patel et al.,

2022). At this stage, muscle activity is still present, and homeostatic activities (breathing, heart rate) are still regular. N1 is usually followed by stage N2.

Stage N2 is the longest sleep stage and consists of about 45 to 50% of total sleep duration. Sleep becomes deeper than in N1, and heart rate and temperature tend to drop (Patel et al., 2022). N2 is represented by two specific brain oscillations: thalamo-dependent spindles (12-15 Hz) and K-complexes. Although spindles are more prominent during N2, they can also be observed during SWS. Spindles are still subject to intensive research and debated conclusions about their role in memory formation. This is mainly due to the variation in their oscillatory frequency (slow spindles from 10-12 Hz versus fast spindles from 13-15 Hz) (Mölle et al., 2011; Marshall et al., 2019), which could provide different contributions to the process of memory consolidation, or the sleep stage they belong to, namely SWS where spindles could promote declarative memory (Clemens et al., 2005; 2006; Laventure et al., 2016) or N2 where they could promote non-declarative memory (Fogel and Smith, 2006; Genzel et al., 2014) and synaptic plasticity (Rosanova and Ulrich, 2005). As mentioned earlier, the N2 sleep stage is also represented by K-complexes, brief (+/- 1 sec) delta bursts (1-4 Hz) that comprise a negative sharp wave, immediately followed by a positive component (Amzica and Steriade, 1997). They are mostly visible in the superior temporal gyri, the cingulum, and the thalamus (Patel et al., 2022). Although K-complex functions are still debated, some studies have provided findings about a potential implication in numerous functions as reported by Gandhi and Emmady's review (Gandhi and Emmady, 2022) such as the maintenance of sleep (Forget et al., 2011) or sudden arousal (Nguyen et al., 2016), depending on how an external stimulus is perceived to be dangerous or not, memory consolidation (Cash et al., 2009), or the maintenance of synaptic homeostasis (Tononi and Cirelli, 2006).

Stage N3, or SWS, is prominent during the first part of the night and represents 25% of sleep duration. It is mostly represented by highly synchronous delta activity (0.5-4 Hz) due to the alternation between global excitation and neuronal silence (Steriade, 2006), though not exclusive to this stage (Dijk, 2009). Known to be the deepest and most restorative stage (Tononi and Cirelli, 2003; Lange et al., 2010), SWS is a stage

during which arousal can be difficult (Patel et al., 2022). SWS is strongly influenced by age, with a decrease in time duration and amplitude as individuals become older (Ohayon et al., 2004). SWS slow oscillations (SO) have been widely investigated due to their crucial role in memory consolidation (Born and Wilhelm, 2012; Rasch and Born, 2013) and the formation of new spines (Chauvette et al., 2012; Yang et al., 2014) according to the Active System Consolidation (ASC) model, or their role in the synaptic downscaling of the neurons (Tononi and Cirelli, 2006; Huber et al., 2006; Vyazovskiy et al., 2008) according to the synaptic homeostasis hypothesis (SHY), two models of sleep and memory that will be detailed later (cf. infra - 1.2.3.3 - Sleep to remember or to forget?).

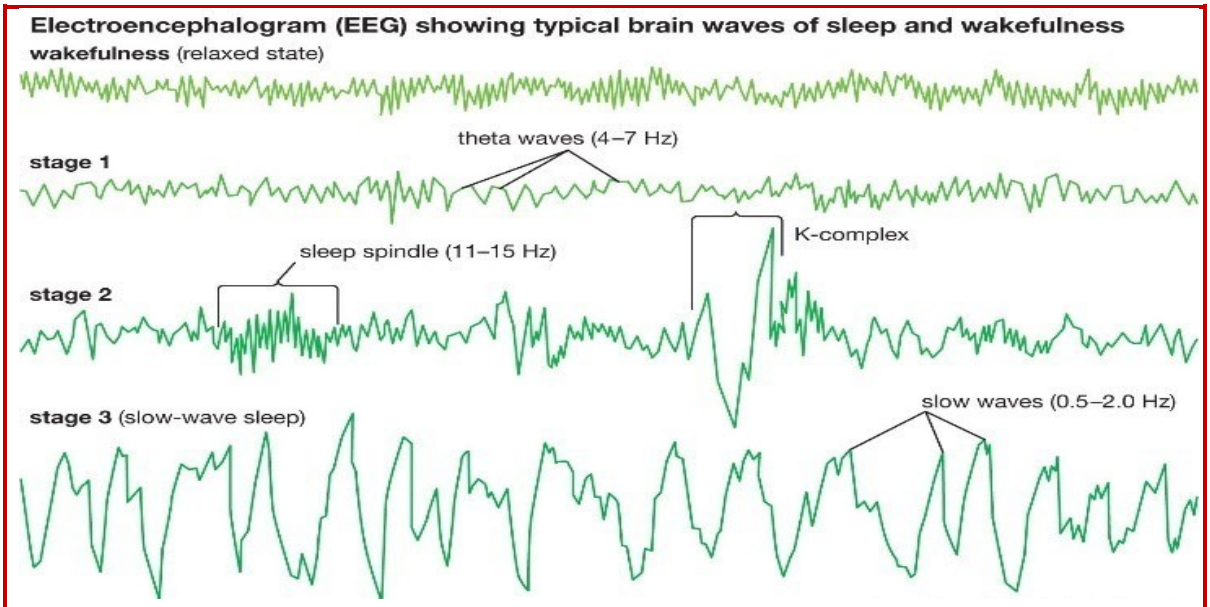


Figure 2: Presentation of sleeping brain oscillations
Source: from Britannica, The Editors of Encyclopaedia. "electroencephalography". Encyclopedia Britannica, 14 Sep. 2022

REM sleep, or the R stage, is the last stage and constitutes up to 20-25% of a total night of sleep. Described in the early fifties and usually called REM sleep (Aserinsky and Kleitman, 1953) or paradoxical sleep in France (Jouvet and Michel, 1960), this stage, for which time duration tends to become more important as the night progresses, is the privileged period for dreams with high emotional valence and nightmares. REM sleep's name comes from the specific eye movements exclusively observed during this stage, contrasting with total muscle atonia besides twitching occurring especially in distal muscles. At the electrophysiological level, high and

desynchronized brain activity is observed. At the physiological level, homeostasis functions are deregulated (Siegel, 2005). Distinctive brain waves from the pons, geniculate nucleus, and occipital area (PGO waves) initially observed in 1957 in anesthetized cats (McGaugh, 2012), can be observed. Although their role is still unclear, they could contribute to memory consolidation (Datta, 2008) and synaptic maturation (Amzica and Steriade, 1996; Li et al., 2017) as a massive concentration of acetylcholine (ACh), a neurotransmitter assumed to foster long-term potentiation (LTP) of the neurons (Teber et al., 2004; von der Kammer et al., 1998), and frontal brain-derived neurotrophic factor (BDNF), a protein involved in the maintenance of memory (Datta et al., 2008) have been reported with PGO waves presence. Finally, studies have reported a high proportion of REM sleep in humans at an early stage of life, suggesting a role in the maturation of the brain (Marks et al., 1995; Frank and Heller, 1997; Blumberg and Seelke, 2010).

3 - From sleep to memory consolidation

From a simple state of protective wakefulness against memory interference to our current knowledge on sleep and its potential links with consolidation and cognitive flexibility, it is reasonable to acknowledge the exceptional evolution of the field of sleep research. While today's major advancements are based on cognitive or computational foundations, the origins can be traced back to the field of clinical research, which indirectly helped establish the fundamental bases of the sleep models we know today.

3.1 - Contribution from retrograde amnesia

The close relationship between sleep and the role of temporal brain regions in the consolidation process of declarative memory originates from clinical reports of amnesic patients whose autonoetic abilities—namely, the capacity to "mentally travel among memories" (Baddeley, 2001; Tulving, 2002)—were impaired (Ribot, 1881; Russell and Nathan, 1946; Sander and Warrington, 1971). Indeed, a gradient, today called the

"Ribot gradient," was illustrated by an increased capacity to recall old memories compared to recent ones and was associated with extensive hippocampal damage (Zola-Morgan et al., 1986; Sutherland and Rudy, 1989; Winocur, 1990) (see Jarrard, 2001 for review). In a seminal study, the authors pointed out how limited damage to medial temporal structures resulted in temporary graded amnesia, whereas extensive damage tended to suppress the gradient, raising for the first time the idea that medial temporal structures become less important over time for the maintenance of explicit memory (Squire and Alvarez, 1995).

3.2 - Hippocampo-neocortical interaction in the process of consolidation

While studies of brain-damaged patients provided insightful information about the importance of temporal brain regions in the process of memory consolidation, the "standard model" (**Figure 3a**) (McClelland et al., 1995; Squire and Alvarez, 1995) and the "multiple memory trace" (MMT) model (Nadel and Moscovitch, 1997) (**Figure 3b**), two opposing models respectively based on animal studies, connectionist simulations, fMRI, and clinical studies, shed light on the interaction between the hippocampus and neocortical brain regions in the ability to recall memories.

The sleep standard model (McClelland et al., 1995; Squire and Alvarez, 1995) emphasizes the role of sleep, especially SWS, in the consolidation process of memories. According to this model, newly encoded experiences are replayed within the hippocampus, leading to a progressive transfer and integration within the neocortex for long-term memory storage. Importantly, the progressive importance of the neocortex in the long-term consolidation process is associated with a gradual withdrawal of the hippocampus in maintaining these memories. In line with the temporal gradient observed in retrograde amnesia, the standard model provides explanations for the phenomenon where recent hippocampo-dependent memories are more susceptible to disruption than consolidated memories that rely on the neocortex.

Comparatively, the multiple memory trace model (Nadel and Moscovitch, 1997) posits that the hippocampus remains involved in the storage and retrieval of episodic

memories, while the neocortex is involved in semantic information and less detailed representations of memories. More specifically, each time a memory is recalled, a new memory trace is created, involving both the hippocampus and the neocortex, resulting in distributed memories across multiple traces, with each trace being a combination of hippocampal and cortical elements. The multiple memory trace model challenges findings about retrograde amnesia and the temporal gradient, proposing that even old episodic memories can be affected by hippocampal damage.

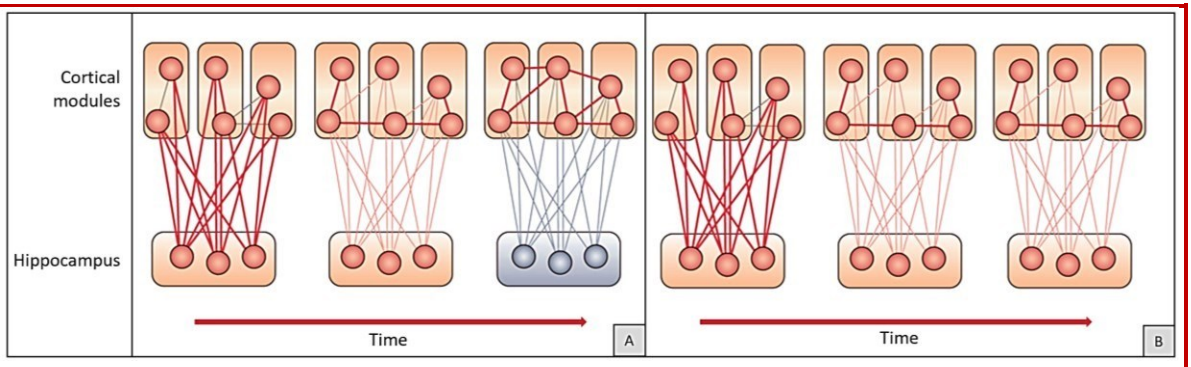


Figure 3: Graphical representations of the cognitive models of memory consolidation. Sleep standard model (a) and the MMT model (b) offer contrasting views on the roles of the hippocampus and neocortex in memory consolidation and storage, the nature of memory traces and the impact upon retrograde amnesia.
(**a**): Representation of the standard model of consolidation. (Source: Frankland and Bontempi, 2005. The organization of recent and remote memories)
(**b**): Representation of the multiple trace transformation theory. (Source: Barry and Maguire, 2018. Remote Memory and the Hippocampus: A Constructive Critique)

Although these models offer diverging perspectives about the hippocampus's role in the ability to recall events, they both laid the groundwork for future models of sleep and memory. These foundational models emphasize the involvement of the medial temporal and neocortical regions in the consolidation of explicit memory, the crucial concept of memory transfer between these two regions, and the maintenance of semantic components that progressively become independent of the hippocampus (cf. infra - 3.3.3 - The first models of sleep and memory).

3.3 - Sleep's role in memory consolidation

While the multiple memory trace model and the standard model brought insightful elements about the mechanisms underlying memory consolidation and interactions

between the hippocampus and neocortex, the question about sleep's influence was raised by the so-called "stability-plasticity dilemma." This dilemma involves the issue whereby temporal and neocortical brain regions could not both contribute to the processes of encoding, consolidation, and recall of declarative information without resulting in massive memory interference or overriding (Carpenter and Grossberg, 1988; Abraham and Robins, 2005). On that basis, the standard two-stage model of memory (Marr, 1971; McClelland et al., 1995) proposed that wakefulness would serve as a crucial period for encoding information dependent on the hippocampus, while sleep would promote the transfer of these encoded events from the hippocampus to the neocortical regions for gradual long-term consolidation. However, the standard two-stage model, like many conceptual scientific breakthroughs, raised more questions than it answered. Among these ongoing debates are the questions of sleep's active versus passive role in memory consolidation, namely whether sleep protects newly formed memories against interference from the environment or serves as a privileged time window for specific physiological mechanisms that contribute to memory consolidation and, assuming the active role of sleep, the contributions of different sleep stages to the formation of long-term memory.

3.3.1 - Sleep's role in memory consolidation: active or passive?

Decades before the standard two-stage model of memory and the association between sleep and consolidation (Marr, 1971; McClelland et al., 1995), sleep benefits were thought to result from protection against interference that could alter recently encoded events. In their study, Jenkins and Dallenbach (1924) aimed to compare the evolution of recall accuracy of nonsense syllables in two participants after 1, 2, 4, and 8 hours of retention, including periods of sleep or wakefulness. While the sleep condition showed performance three times higher than a similar period of wakefulness, they concluded that the difference resulted from the preventive effect of sleep against external interference that could conflict with newly encoded memories. This led to the theory that sleep's role in memory consolidation is passive. According to this theory, sleep provides a state where interference from new sensory input is minimized, allowing memory consolidation processes that began during wakefulness to continue

uninterrupted. The brain is less exposed to external stimuli and new information during sleep, reducing interference and allowing for the uninterrupted processing and integration of memories encoded during wakefulness. Moreover, the reduced cognitive load during sleep is thought to give the brain the opportunity to stabilize and strengthen memories. Finally, the theory posits that even if overall reduced neural activity and metabolic demands during sleep create a favorable environment for memory consolidation, it does not imply that sleep actively facilitates these processes. These arguments were addressed by numerous studies (Ellenbogen et al., 2006; Ellenbogen et al., 2009; Piosczyk, 2013; Zhang et al., 2022). Although results from Ellenbogen's research revealed a significant sleep benefit, two important concerns can be raised. First, the offline period between encoding and recall was not controlled, leading to potential interferences or cueing effects during the incubation. Second, since the studies were only behavioral, no physiological output that could correlate with the behavioral performances was provided. Four years later, these considerations were controlled in a sleep study using EEG recording and a controlled incubation time between encoding and recall (Piosczyk, 2013). Interestingly, no significant difference between sleep and wake conditions was reported. Among the different sources of explanations for the lack of significance (age of participants - 16 years old, their sex - all female), the design of the study (participants' training and testing sessions were separated by a nap instead of a full night of sleep and a week between conditions) can be raised. Indeed, a recent study (Zhang et al., 2022) that compared different incubation durations after encoding (30 min, 12 h, and 24 h) only reported a sleep benefit after 12 hours of incubation. Finally, in a recent study, sleep was shown to significantly improve rule abstraction but only a week after learning (Pereira et al., 2023).

3.3.2 - Sleep to remember: REM sleep versus nREM sleep contribution

The last decades of sleep research were ripe not only for innovative cognitive models about memory consolidation but also crucial findings about the specificities of sleep stages. Fostered by technological advancements (polysomnography and neuroimaging), early sleep research in the mid-20th century identified different stages

of sleep, notably REM sleep (Aserinsky and Kleitman, 1953). Investigations and comparisons between nREM and REM sleep soon revealed strong biological, physiological, and homeostatic differences (Jacobson, 2022) (Table 1), leading to the question of how those two stages could also differ in their role in cognitive functions, including memory.

Table 1 | nREM sleep versus REM sleep

	Differences	
	nREM sleep	REM sleep
Sleeping brain physiology		
Brain waves	. Low frequency . High synchronization	. High frequency . desynchronized
Timing	. First part of the night	. Second part of the night
Brain activity	. Decreased from wake	. Increased in motor and sensory areas
Movements		
Eye movement	. No movements	. Movements around all directions
Muscles	. Similar to wakefulness	. Muscle atonia
Homeostasis		
Heat rate	. Slow and steady	. High and irregular
Respiration	. Slow (15% compared to wake)	. Increased
Blood pressure	. Decreased from wake	. Increased from wake
Body temperature	. Regulated at lower set point than wakefulness	. Not regulated . No shivering or sweating

The question about the specificity of each sleep stage upon the mechanism of consolidation was illustrated by the dual process hypothesis, promoting an independence between nREM and REM sleep and the sequential hypothesis that posits a mutual influence upon memory consolidation.

According to the dual process hypothesis, nREM sleep and REM sleep would act independently from each other, thus promoting different memories (Gais and Born, 2004; Rauchs et al., 2005; Born and Wilhelm, 2012; Rasch and Born, 2013). Based on the difference between the first and second part of the night, respectively represented by a higher amount of nREM sleep and REM sleep, the dual process hypothesis posits that nREM sleep would be the support of declarative memory, whereas REM sleep

would promote non-declarative memory. Such a paradigm of separation was mostly tested by studies that used sleep deprivation protocols (Barret and Ekstrand, 1972; Plihal and Born 1997; Wagner et al., 2002). Technically, depending on the type of memory tested, the participants were selectively deprived during the first or second part of the night to promote a majority of nREM or REM sleep. At this stage, it is crucial to raise how sleep deprivation is not without side effects, susceptible to alter the trustfulness of the conclusion from studies using this method. Indeed, numerous studies revealed how sleep deprivation could impair not only concentration, vigilance, and mood, but also the immune system, working memory system, and circadian rhythms like glucocorticoids (Durmer and Dinges, 2005; Killgore, 2010; Davies et al., 2014). A less outright and more subtle approach raised the hypothesis whereby both nREM and REM sleep could be involved in declarative memory consolidation but not the same aspects. Concretely, nREM sleep would be related to the semantic and episodic component of the memory, REM sleep would be associated with the emotional one. This approach was supported by numerous studies that reported an important influence of REM sleep in emotional memory (Groch et al., 2013), irrespective of whether the type of material was words (Wagner et al., 2001) or pictures (Hu, and al., 2006; Nishida et al., 2009). Interestingly, REM sleep benefits upon emotional memory were sometimes found to last for years (Wagner et al., 2006) (for review, see Genzel et al., 2015).

In line with the complementary roles of nREM and REM sleep, the sequential hypothesis, presented as an alternative, suggested that the combination and sequence of nREM and REM sleep stages are vital for the overall benefits of sleep (Giuditta, 1977, 1985; Giuditta et al., 1995) (for review, see Giuditta, 2014). The sequential hypothesis takes its origins from a preliminary assumption whereby nREM sleep and especially SWS, would be strictly associated with physiological synaptic restoration (Walker and Berger, 1980; Shapiro et al., 1981) and REM sleep with learning and memory acquisition (Fishbein and Gutwein, 1977; Pearlman, 1979). At first sight, this perception of sleep stages makes sense. Indeed, it has been observed that the concentration of brain pyruvate and lactate tended to change depending on the degree of intensity of waking activity (Horne, 1981). Secondly, ontogenetic observations

revealed the interesting trend whereby REM sleep proportion was much higher in newborn humans than adults, suggesting that REM sleep would play a crucial role in synaptic formation and brain development (Roffwarg et al., 1966). On that basis, the sequential hypothesis went further by proposing the concept of "two step mechanism of memory processing" (Ambrosini and Giuditta, 2001). Concretely, (1) nREM sleep, and especially SWS, would be involved in the synaptic downscaling, resulting in the removal of irrelevant memory traces. (2) REM sleep would promote the integration and consolidation of newly acquired memories. The degree of memory consolidation efficiency would be the result of that cyclic nature of the interactions between nREM and REM sleep. Concretely, overall benefits upon memory consolidation would result from a repeated and cyclic alternance of nREM sleep and REM sleep stages (Ambrosini and Giuditta, 2001). The sequential hypothesis has been supported by numerous studies in rats (Ambrosini et al., 1992, 1995) and humans (Stickgold et al., 2000; Mednick et al., 2003).

This preliminary introduction was important to understand how the perception of sleep progressively moved from a "passive stand-by mode" to a crucial period for memory and the consolidation process. Decades of questions and research from various fields (clinical, biology in humans and animals) led to a convergence between the cognitive mechanisms (standard model versus multiple trace transformation theory) and the physiological manifestations of sleep stages in nREM and REM sleep (dual process versus sequential hypothesis) to propose a global framework of memory consolidation. At this stage, a brief summary about these last two models of sleep stages is matter of importance since they can be reasonably considered as the cornerstone of the most recent and promising technics of investigation of sleep in memory integration (cf. infra - 4.3 - Sleep and neural replay).

The dual process hypothesis has significantly advanced understanding of memory consolidation by proposing that non-rapid eye movement (nREM) sleep and rapid eye movement (REM) sleep play distinct and complementary roles. This approach, still ongoing debate, was crucial by highlighting the unique contributions of different sleep stages to memory processing. However, this hypothesis was not without a major

limitation. Indeed, by treating nREM and REM sleep as dual and independent processes, the dual process hypothesis overlooks the intricate interplay between these stages. This limitation was addressed by the sequential hypothesis of memory that posited a dynamic interplay between nREM and REM sleep, where memories would be initially processed and stabilized during nREM sleep and subsequently consolidated during REM sleep. However, and despite its advances, the sequential hypothesis does not really answer about the crucial question about the specific mechanisms in nREM or REM sleep that could contribute to the progressive consolidation of memory. In the early 2000th, two models were proposed to fill this gap: the active system consolidation driven by a physiological approach and the synaptic homeostasis hypothesis, focusing on the biology.

3.3.3 - Cognitive models of SWS: Focus on Slow oscillations

Building on the foundational models of memory transfer from hippocampus and neocortex and the role of nREM sleep proposed by the dual process hypothesis, recent research has introduced the Active Systems Consolidation (ASC) model. According to the ASC model, during sleep, memories would be repeatedly reactivated in the hippocampus and progressively transferred to the neocortex through a highly synchronous brain activity. It is important to raise that ASC (**Figure 4**) posits that only SWS would be involved in the consolidation of declarative memory (Marshall and Born 2007; Diekelmann and Born 2010; Born and Wilhelm, 2012; Rasch and Born, 2013). Concretely, newly acquired events during wake would be encoded within both hippocampus and neocortical areas. Subsequently, SWS would foster the reactivation of these events and their gradual distribution from temporal to neocortical regions for a long-term consolidation. The transfer would be driven by a highly synchronous activity, including the neocortical oscillations, the thalamo-cortical spindles phase-locked with the SO up-phase, and the sharp wave ripples from the hippocampus phase-locked with the spindles' trough. ASC model is supported by a large body of studies that revealed the presence of the SO timeframe representation in the visual cortex or in neocortical regions (Ji and Wilson 2007; Euston et al., 2007).

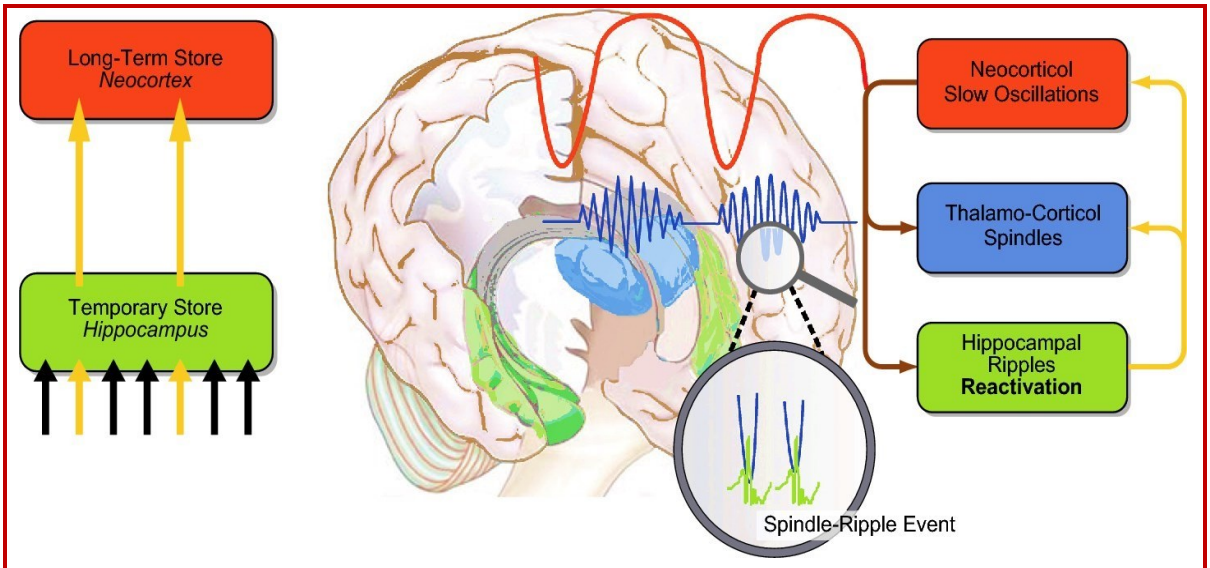


Figure 4: Representation of the active system consolidation during sleep. Newly formed declarative memories during wake are temporarily stored in hippocampus (green) and progressively transferred to the neocortical areas (red) for a long-term storage across multiple reactivations. The transfer from hippocampus to neocortex is mediated by a synchronous activity occurring during SWS. The dialog between hippocampus and neocortex would be controlled by slow wave oscillations (red line), whereas ripples (green line) and spindle (blue line) would be involved in memory reactivation. The cortico-hippocampal communication is regulated by slow oscillations in the neocortex (red), which trigger repeated reactivations within the hippocampus. These reactivations are marked by hippocampal sharp wave ripples (green) that coincide with the excitable troughs of sleep spindles (blue oscillations), creating a "spindle-ripple interaction." This interaction is embedded within the depolarizing up-phase of the slow oscillations, facilitating the transfer of hippocampal memories to the neocortical networks and thereby supporting memory consolidation.
(Source: Rasch and Born, 2013. About sleep's role in memory – Original source: Born and Wilhelm, 2012)

Some studies also pointed out an increase of SO, ripples and spindles after encoding (Gais et al., 2002; Mölle and Born, 2009) and a causal link with a better memory retention (Huber et al. 2004; Clemens et al., 2005; 2006; Girardeau, et al., 2009; Girardeau and Zugaro, 2011). Human studies also supported the link between the SO and the consolidation of explicit memory by using SO up-state close-loop stimulations (Ngo et al., 2013) or targeted-memory reactivation (TMR) (Cairney et al., 2018) (cf. infra, chap. 4.3.3 – Promoting reactivation during sleep: emergence of TMR). Tough it is important to raise again the fact that ASC model do not incorporates REM sleep into the equation of memory consolidation, which sounds like a "step-back" to the dual hypothesis, this influential model proposes a rich explanation about the interaction between hippocampal and neocortical areas and the brain activity behind it. However, ASC was not the unique model that focused on slow oscillations to explain the relationship between sleep and memory formation. Indeed, another influential model

in the field of memory consolidation is the Synaptic Homeostasis Hypothesis (SHY), which offers a different perspective on the role of sleep, based on biology.

The synaptic homeostasis hypothesis (SHY), was proposed by Tononi and Cirelli (Tononi and Cirelli, 2003, 2006) (**Figure 5**). SHY is based on the postulate that during wake, encoding process would result in a synaptic strengthening, illustrated by a progressive potentiation of these synapses, and thus, energy consumption. Hence, during SWS, SO would serve the crucial function in downscaling potentiated synapses that would return to an acceptable basal potentiation in terms of energetic cost and tissular volume (for review. see Bertran et al., 2013). In this view, downscaled synapses would be operational again for future encoding. The second crucial point is that the downscaling would be proportional to the level of potentiation, in a sense that synapses would keep traces of their "experience". SHY was supported by histological studies that revealed the relation between SO and long-term depression (LTD) (Barrionuevo et al., 1980; Mascetti et al., 2013). Although most of the studies that supported SHY are in animals (Vyazovskiy et al., 2008, 2009; Tononi et Cirelli, 2014), elements of proofs were also found in neuroimaging studies in humans (Takashima et al., 2006; Gais et al., 2007).

The interesting approach from SHY comes from the fact that it appears "against the tide". Indeed, the biological approach focusing on synaptic homeostasis instead of memory consolidation sounds like an antagonist model. Indeed, the question here is not even to understand how nREM sleep or REM sleep could contribute to the formation of memory. Slow oscillations would only serve for the preservation of synaptic mechanisms.

Building upon the presentation of SHY and ASC models, both the Active Systems Consolidation (ASC) model and the Synaptic Homeostasis Hypothesis (SHY) underscore the importance of sleep and especially the slow oscillations. However, they diverge in their core mechanisms and emphases.

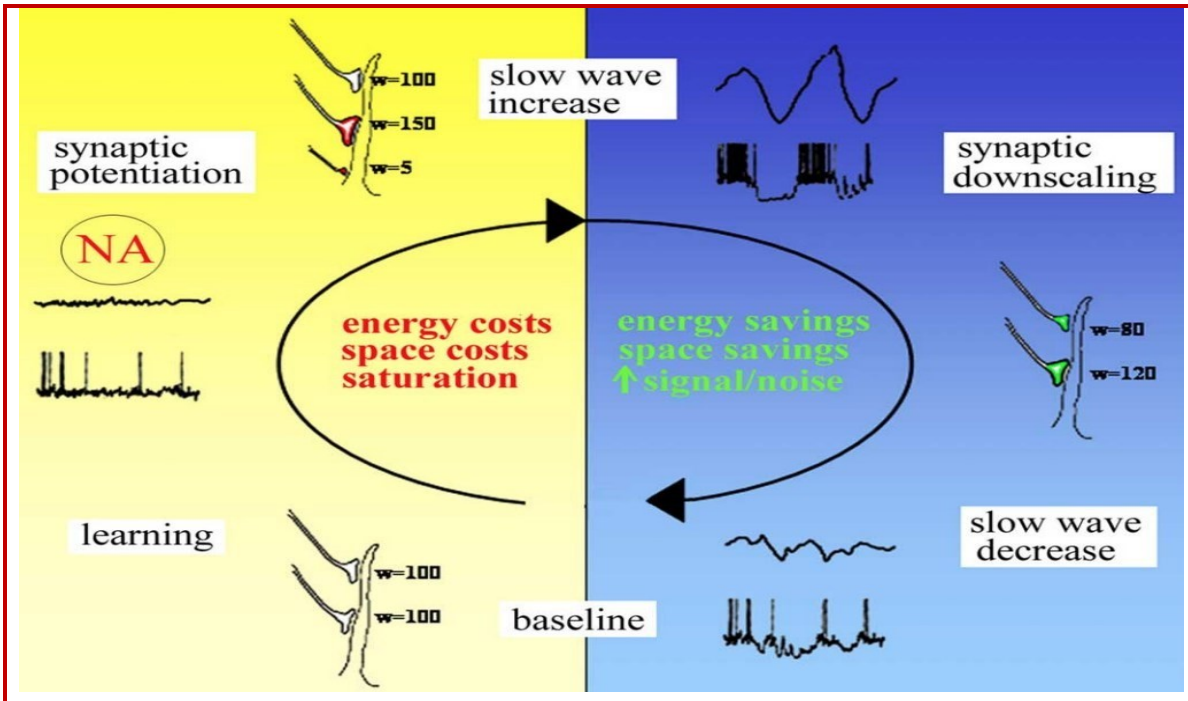


Figure 5: SHY. SWS would foster synaptic downscaling of neurons involved during encoding. One must point out that after sleep, the strength of the potentiation is still maintained.
(Source: Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. Sleep medicine reviews, 10(1), 49-62.)

Indeed, the ASC model focuses on the reactivation of memory traces and the subsequent transfer from the hippocampus to the neocortex, highlighting a process of selective strengthening and integration. Comparatively, SHY model emphasizes a global synaptic downscaling process during sleep, which is thought to maintain overall synaptic efficiency and neural homeostasis. These differences raise a passionate debate in the field about whether sleep's primary function in memory consolidation is to selectively enhance specific memories or to ensure the overall stability and functionality of neural networks through synaptic renormalization (Sara, 2017; Poe, 2017). To conclude, it is also possible to extract converging points between ASC and SHY models. Indeed, an MRI study from Mascetti (Mascetti et al., 2013) pointed out that pre/post sleep contrast revealed an activation of new brain areas after sleep, correlated with performances, suggesting a reorganization of mnesic traces, in line with the ASC. On the other hand, the results also revealed that the reactivation of brain areas involved in the encoding process was proportional to the amount of SO, in line with the SHY. On that basis, it is not excluded that downscaling and consolidation both occur at the same time during sleep, but within different brain

regions, suggesting that memory processes during sleep may be heterogeneously distributed within the brain.

4 - Sleep and relational memory

The previous section has raised how the early 2000th were the stage for intense and passionate debate about the cognitive dynamics behind the process of memory consolidation, how sleep could contribute to consolidate memory, and more specifically, what sorts of physiological mechanisms could interact and promote it. Through the presentation of the dual process and the sequential hypothesis, the ASC and SHY models, the research scope of field has been shown sometimes polarized with the antithetical points of view between the role of nREM or REM sleep, sometimes converging with the ASC and SHY models that both highlighted the role of slow oscillations during sleep but for different reasons. However, science history has often proven that between the extreme, the "truth" (assuming that truth itself exists), or better said, the reason, often lies somewhere in between. Said differently, it is reasonable to expect a situation, a model, that could be susceptible to bind the concept of the mutual role of nREM sleep and REM sleep with complementary mechanisms, the concept of transfer and reactivation of memory, and the downscaling or the transfer promoting role of slow oscillations. However, such a purpose needs to modify the point of view associated with memory and consolidation.

4.1 - Sleep and cognitive flexibility

Over the previous sections, memory was presented as a material, immutable, limited and almost measurable. Indeed, according to the previous models, an event, sometimes called engram, would be experienced during wake, temporarily stored in a compartment most of the time called hippocampus, and finally, transposed into another one during the night, called neocortex. While it sounds reasonable to raise the extreme simplicity of this presentation, it also sounds crucial to highlight that in such a scenario, the brain would not differ from a simple hard disk, a computer

(McGaugh, 1966). However, decades of intensive research (**for review. see LeDoux, 2022**) have proven that beyond the conception of memory consolidation, events could also experience different types of modulation, like disruption (Briggs et al.,2007; Briggs and Riccio, 2007), enrichment (Lee, 2009; Rudy et al., 2002) or distortion (Loftus et al., 2017).

This conception of memory allows to reconsider it as modular, a reflect of cognitive flexibility, namely adaptive strategies applied to face with continuously changing environments and unusual situations. Cognitive flexibility can be described as part of a more global concept, namely creativity, which can be defined as the ability to produce something new, original, and appropriate to solve an issue (Sternberg, 1995; Dietrich, 2004; Runco, 2004). The cognitive flexibility relies on the ability to manipulate episodic and semantic representations, or schemas. A schema can be defined as ensembles of "cognitive features", or gist, that events have in common with each other (Zeithamova et al., 2012, Preston and Eichenbaum, 2013) (**Figure 6**) and can be interpreted as a "cognitive stereotype" that aims to categorize and structure the environment. Since a simple example is most of the time more comprehensive than exhausting definitions, one can imagine someone experiencing for the first time a birthday and Christmas parties. These events, rare in time (once a year) will be considered as two different schemas, with specific codes or rules (maybe a dress code, cooking specific recipes…) and rituals (music, gifts…) (**Figure 6**). However, these schemas also share codes and rituals similarities. These codes or rituals are called "gist". In this example, common gists appear, like "MUSIC" and "GIFT". Now, if a new experience that shares the gist "party" with birthday and Christmas celebration occurs, like a "cocktail party", maybe that same person will expect to receive presents. Beyond the potential deception, that person will have to use its adaptive cognitive flexibility and create a new schema called "cocktail party", containing specific codes (alcohol, dress code…) to avoid experiencing a similar deception next time.

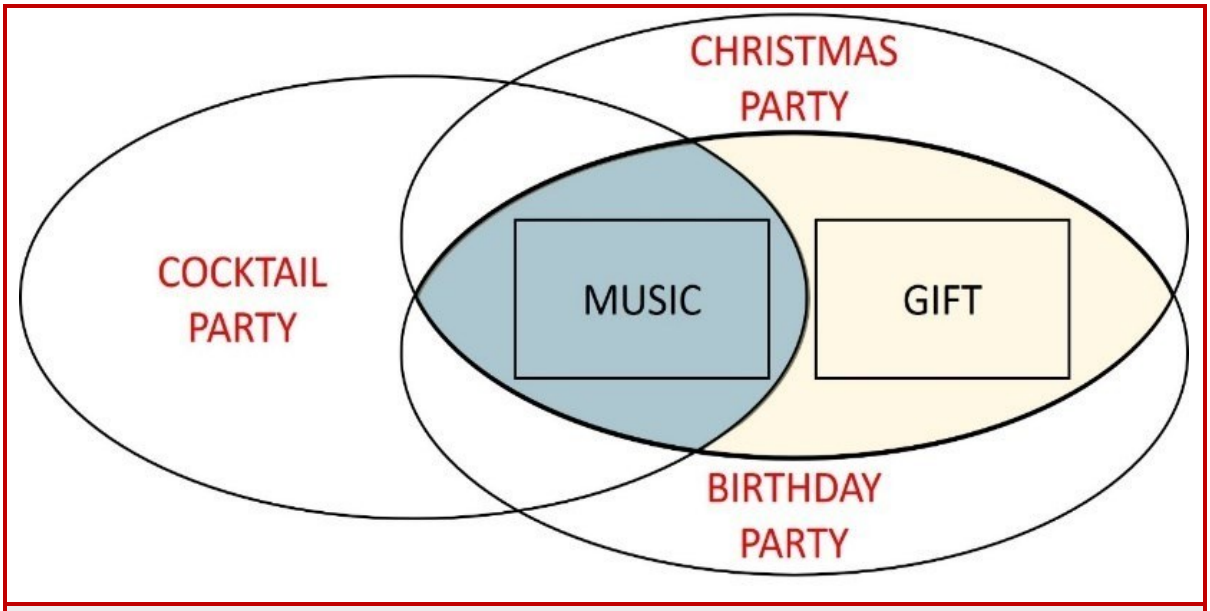


Figure 6: Schematic representation of the schema building and the gists. Here, "MUSIC" and "GIFT" are two gists shared by the cognitive schemas "CHRISTMAS PARTY" and "BIRTHDAY PARTY". However, only "MUSIC" is associated with the new schema "COCKTAIL PARTY". This distinction leads to the creation of one specific schema: "PARTY".

The cognitive process as well as the physiology behind the formation of a new schemas susceptible to share gist with each other were integrated into the so-called framework of sleep "Information overlap to abstract" (iOtA). The model iOtA designed by Lewis' team (Lewis and Durrant, 2011) posits that during SWS, experiences that share a lot of common components (gists) would be strengthened, resulting in the formation of new schemas, whereas experience that only comprise of idiosyncratic representations would be downscaled (**Figure 7**). A global comprehension of the key points of the model requires to break it.

Information Overlap (iO):

During wake, new information that often overlaps with previously stored knowledge can be encoded. This overlap is detected and marked for further processing during sleep. This marking can be described as a synaptic tagging whereby specific synapses in charge of encoding overlapping events are tagged for further strengthening or modification during subsequent nREM sleep, especially SWS. During this stage, the hippocampus and neocortex interact to reorganize and integrate new memories.

To abstract (tA):

During SWS, the interaction between hippocampus and neocortex would lead to the formation of more generalized and abstract representations. This involves integrating

new information with existing knowledge and extracting commonalities, which enhances the brain's ability to understand and predict the world. The result is the formation of new schemas, cognitive frameworks that help organize and interpret information.

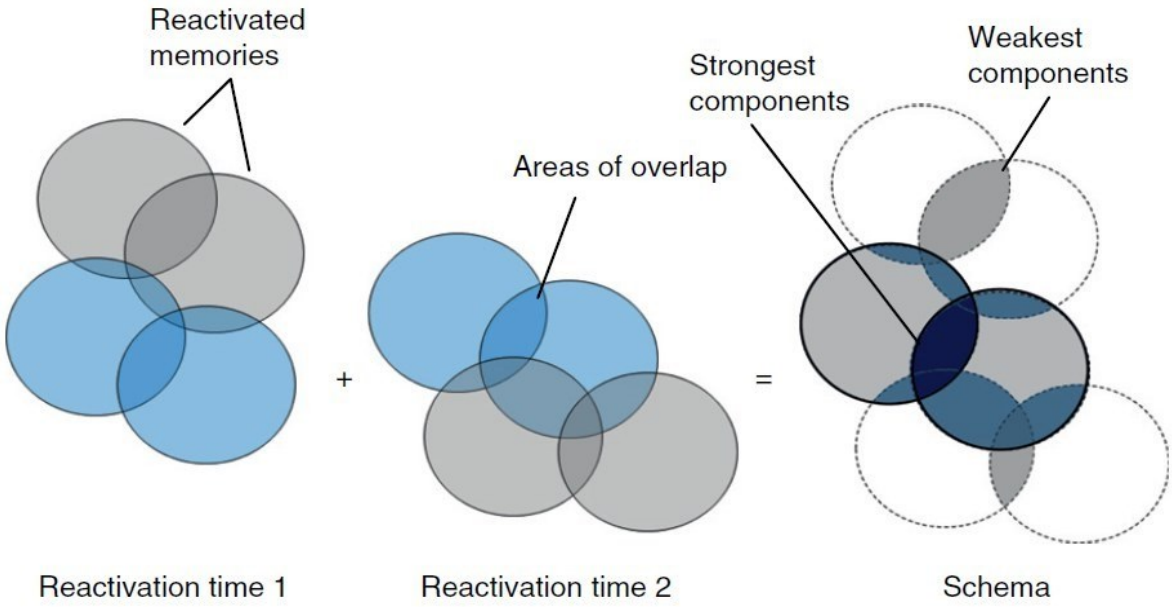


Figure 7: Schematic representation of the iOtA model. Here, memories that shares common events are strengthened whereas unitary events are downscaled. This transformation of memory is assumed to lead to schema formation. Circles represent replayed memories. Overlapping areas represent the relationship between new and old memories. (Source: Lewis and Durrant, 2011. Overlapping memory replay during sleep builds cognitive schemata).

The key mechanism of support is the reactivations of brain areas involved in the formation of the event during wake and the neural replay mediated by the hippocampo-neocortical connection (Laroche et al., 2000; Colgin, 2011; Fell and Axmacher, 2011; Sharon et al., 2011), especially the medial prefrontal cortex (mPFC) (Grossberg, 1987).

The iOtA model was later extended to the "Broader Information Overlap to Abstract" or BiOtA (Lewis et al., 2018) in order to provide a more comprehensive framework of interaction between nREM sleep and REM sleep in the integration of memory (**Figure 8**). A crucial novelty here is the implication of REM sleep in the transformation and integration of newly formed representations, resulting in enriched representations. This modulation would be possible due to the high level of ACh that fosters high levels

of calcium (Ca2+) influx and PGO waves (Lewis et al., 2018).

Here again, it is required to split the concepts for a full comprehension.

Broader Information Overlap (bIO):

BiOtA model extends the detection of overlapping schema not only for declarative and procedural memories but also across different types of cognitive processes and domains, including emotional experiences, skills, and various types of learning. Concretely, sleep would promote the integration of information across different cognitive domains, enhancing the brain's ability to form more complex and abstract representations. Moreover, while SWS keep being crucial for declarative memory consolidation and integration, it would also play a role in cognitive functions like problem-solving and planning by allowing the brain to process and integrate complex information. However, the major difference from iOtA is the integration of REM sleep as the cornerstone of synaptic plasticity and integration of memory.

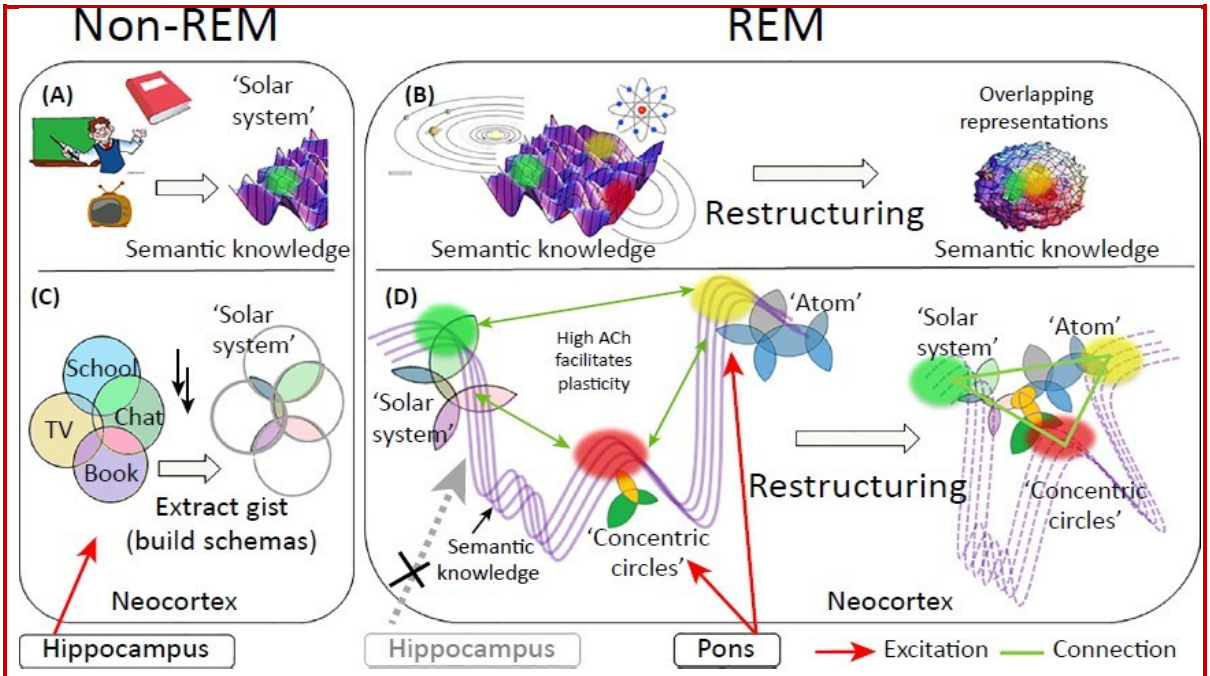


Figure 8: Schematic representation of the BiOtA model. (**a**) During wake, the representation of the semantic knowledge about space is shared between teaching lessons, books, and TV. (**b**) A new representation of the atom with concentric circles will restructure the representation of space during REM sleep. (**c**) At the functional level, the replay induced by the hippocampal and neocortical dialog during SWS leas to the overlapping of newly formed gists and old ones that will potentiate representations shared between old and new gists whereas unitary representations will be downscaled. (**d**) During REM sleep, PGO waves and high level of ACh fosters the detections of similarities between gists and the formation of new schemas. These new representations are assumed to promote the emerging of new concepts and semantic knowledge.
(Source: Lewis and al., 2018. How Memory Replay in Sleep Boosts Creative Problem-Solving).

This integration echoes findings about REM sleep that has been shown to promote the secretion of "Brain-Derived Neurotrophic Factor" or BDNF, involved in the neurogenesis process. These results were both found in rodent (Ambrosini and Giuditta, 2001; Giuditta, 2003) and human studies (Ficca et al., 2000; Gais et al., 2000; Stickgold et al., 2000). In addition to procedural and emotional memory consolidation, REM sleep would support creativity, problem-solving, and the abstraction of complex patterns. Indeed, REM sleep has been shown to be involved in a wide range of cognitive skills, comprising of foreign language learning (De Koninck et al., 1989), studying (Smith and Lapp, 1991; Meienberg, 1997), but also semantic (Meienberg, 1977; De Koninck, 1991; Smith and Lapp, 1991), visual (Zimmerman et al., 1970), motor (Buchegger and Meier-Koll, 1988, Buchegger et al., 1991), and auditory memory (Verschoor et al., 1984), was shown to play a crucial role in memory and cognitive reshaping (Schacter et al., 2012; Schlichting and Preston, 2015) or in executive functions abilities like mental flexibility, inhibition and planification (Postle, 2006; Ranganath and Blumenfeld, 2009; Llewellyn, 2016; Schönauer et al., 2018).

To Broader Abstraction (tBA):

Importantly, sleep is assumed to facilitate not only the abstraction of overlapping information within the same domain but also across different domains. This leads to the formation of more generalized and versatile cognitive frameworks. The consequence is the formation of more complex schemas, which are necessary for higher-order cognitive functions like critical thinking, creativity, and innovation.

BiOtA model can be perceived as a global integration of SHY and ASC models by incorporating elements from both theories. From ASC, BiOtA model integrates the idea that specific experiences are reactivated during SWS, leading to the strengthening and integration of important memories from the hippocampus to the neocortex. From SHY, the model also acknowledges the global synaptic downscaling that occurs during SWS from synapses that support the encoding of idiosyncratic elements, which helps maintain synaptic balance and overall brain homeostasis. However, BiOtA extends the simple concept of consolidation by emphasizing the abstraction of overlapping information, and the progressive integration which helps in forming generalized concepts and schemas.

4.2 - Focus on transitive inference

The role of sleep in enhancing cognitive schemas for the development of more adaptable and enriched mental representations is widely recognized, though the underlying mechanisms remain unclear. The familiar advice to "sleep on it" when faced with perplexing problems is not without merit. After a full night's rest, problems tend to be approached with a fresh perspective, replacing emotions and uncertainty with analytical clarity and insight (Bowden et al., 2005; Luo and Knoblich, 2007; Kumaran, 2013). This insight is closely linked to a holistic cognitive function known as transitive inference (TI), which involves the ability to form new conclusions or strategies based on given premises. As an example, assuming a premise A "do my homework" related to the heuristic B "pass my exam" and C "being graduated", it is possible to "jump" from A to C and infer that if "I do my homework, I will be graduated". At the more experimental level, TI is usually assessed by using series of items that are hierarchically related (**Figure 9**).

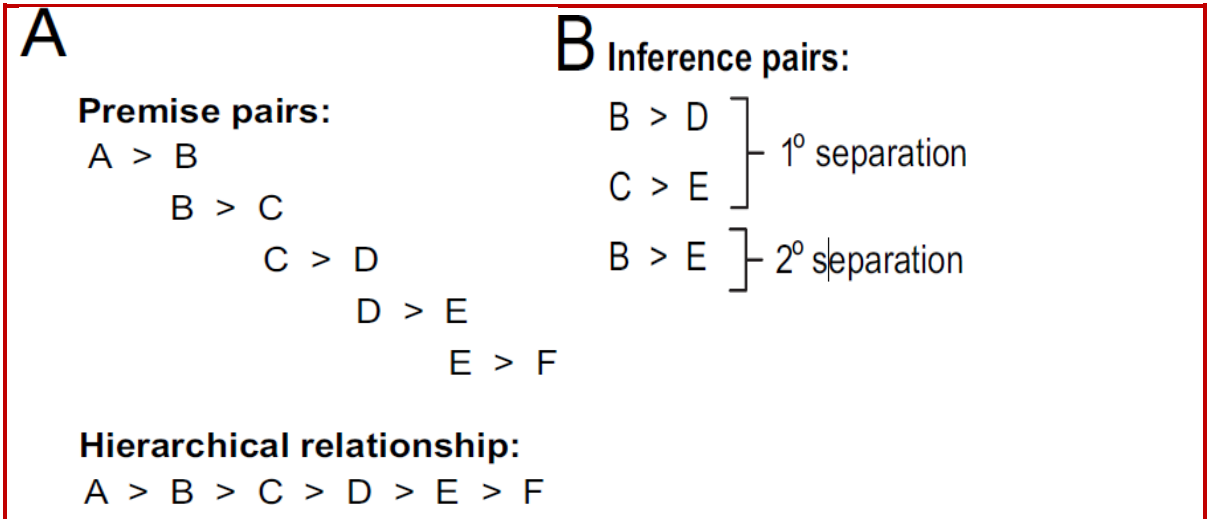


Figure 9: Representation of the overall concepts from transitive inference. Premise pairs refer to combinations of successive items within a hierarchy. Inference pairs are built upon distant items. In a series from A to F, pairs that comprises of A and F (e.g., AB or CF) are called anchor pairs and are usually separated from other pairs as there are usually associated with a higher accuracy due to the fact that A is always dominant and F is always submissive.
(Source: Ellenbogen et a., 2007. Human relational memory requires time and sleep.)

Within a series of items (e.g., A.B.C.D.E), the participants are expected to learn associations about overlapping premise elements (AB, BC, CD, DE) with trial error reinforcement. If A and B are presented, participants are expected to guess that A is dominant and B submissive, but without being informed about the hierarchy. In a second time, new pair associations are presented (inference pairs) (e.g., A-C) and participants are expected to infer the hierarchy between A and C. Regarding the impact of sleep on TI, a notable behavioural study investigated this aspect (Ellenbogen et al., 2007). The results revealed an increase of performance at delayed session 12 hours after learning, supporting the idea that time is essential for creating relational memory. Interestingly, the results also showed an increase after 24 hours but only for inference pairs with two degrees of distance (e.g., B-E) compared to one degree only (e.g., B-D). This distance effect is known as the symbolic distance effect (SDE) name. The SDE is supported by a large body of studies from multiples fields of research using colours (Trabasso et al., 1975), numbers (Shepard et al., 1975), or even behaviour (Potts, 1972). According to numerous studies, the reason of the presence of SDE would depend more on how individuals perceive the elements (Potts, 1974; Moyer and Bayer, 1976; Hamilton, 1978; Scarf and Colombo, 2008) than real distance between these elements. More precisely, the way an element is perceived by its components (shape, colour, size...) would define its position within the hierarchy. The results from Ellenbogen' study were replicated and confirmed by a study that did not only support the sleep and SDE effects on TI observed in Ellenbogen' study (Ellenbogen et al., 2007) but also revealed a significant improvement of TI accuracy when training was associated with reinforcement and feedback (+31.08% for the sleep group and 23.07% for the wake group) (Werchan and Gomez, 2013).

At the functional level, parietal (Goel et al., 2009), temporal (Heckers et al., 2004; Greene et al., 2006; Goel et al., 2009) and neocortical brain regions (Goel et al., 2009; Wendelken and Bunge, 2010; DeVito et al., 2010; Koscik and Tranel, 2012) were found to be engaged in relational memory processing. If the idea whereby neocortical - in particular the rostrolateral prefrontal cortex (RLPFC) is engaged in relational memory is widely accepted, surprisingly, the conclusions about the implication of the hippocampus appeared less clear. Indeed, a study run by Wendelken and Bunge in

2010 did not find any engagement from hippocampus in TI process. In 2020, a study that aimed to assess the role of hippocampus during logical reasoning and belief bias based on age, compared accuracy from "young" versus "old" groups. A significant activation was found within the hippocampus during logical processing but only for the "old" condition (Ziaei et al., 2020). Numerous studies have provided insightful explanations about the conditional involvement of hippocampus in cognitive flexibility. As an example, the level of awareness of the hierarchy between items was found to influence hippocampus activation (Martin and Alsop, 2004; Greene et al., 2006; Libben and Titone, 2007; Lazareva and Wasserman, 2010), although the definition and assessment of awareness was shown to differ between the studies. Level of awareness was not only shown to predict hippocampus activation but also behavioural performance (Martin and Alsop, 2004). In this study, after being evaluated by a questionnaire, the participants defined as "aware" exhibit a higher accuracy compared to the "less aware" group (Martin and Alsop, 2004). Similar findings about the level of awareness (Lazareva and Wasserman, 2010) as well as the efficiency of the strategy used (Libben and Titone, 2007) and the positive effects upon accuracy were presented.

4.3 - Sleep and neural replay

Excepted dissenting voices (Vertes, 2004; Vertes and Siegel, 2005), it is widely accepted that sleep and memory consolidation are heavily interrelated. In view of the multiple hypothesis and models proposed to explain such a relationship, it is reasonable to admit that the exact reasons why memory consolidation is fostered by sleep is still unclear. However, and although these models are competing or complementary with each other, they all share the same position about the critical importance of memory reactivation.

4.3.1 - Origins of neural replay during sleep

In 1989, Pavlides and Winson demonstrated that hippocampal place cells activity coded for space and orientation when rats were placed in a novel environment

(Pavlides and Winson, 1989). They also noticed an increase of firing rate during sleep from place cells involved during wake. The concept of replay during sleep emerged. However, it is in 1994 that Wilson and McNaughton experiment in rodent place cells raised the concept of representations (Wilson and McNaughton, 1994). Concretely, they revealed that place cells coding during wake resulted in a modulation of the firing patterns within pyramidal cells that could be detected during SWS (**Figure 10**). From a recording of 42 random place cells, it also appeared that cell pairs that tended to fire together before sleep also fired together after sleep.

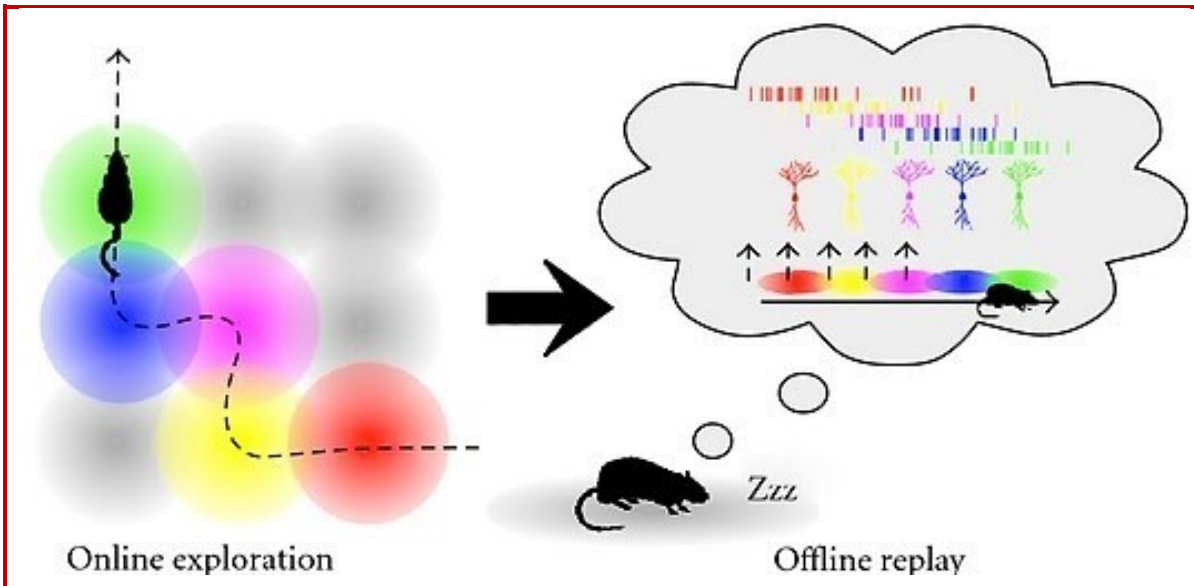


Figure 10: Representation of the concept of replay. Patterns of spatial exploration encoded within place cells during wake are replayed during SWS and REM sleep.
Source: Sadowski et al., 2011. Ripples Make Waves: Binding Structured Activity and Plasticity in Hippocampal Networks.)

Decades of research have completed Wilson and McNaughton's findings. As an example, it has been observed that the replay of sequential patterns during SWS was a compressed version of the firing observed during wake (Lee and Wilson, 2002; Ji and Wilson, 2007). Spontaneous reactivation of firing patterns was also shown to decrease after learning (Battaglia et al., 2005). At the electrophysiological level, firing replay and subsequent transfer were shown to mainly depend on the ripples (Girardeau et al., 2009; Girardeau et al., 2014) as their suppression was shown to impair memory consolidation (Girardeau et al., 2009). Although the research field about sleep and memory replay is mostly covered by research on SWS, REM sleep has

also been shown to play a role in memory replay and consolidation, but at a more subtle and indirect level than ripples during SWS. Indeed, it has been shown that the occurrence of spindles and ripples during SWS was correlated with the number of changes of firing rate within the hippocampus during REM sleep episodes following SWS (Grosmark et al., 2012; Miyawaki and Diba, 2016) (for review, see Tang and Jadhav, 2019). While Tang and Jadhav only focused their analysis on the homeostatic role of REM sleep, raising the possibility that "the synaptic homeostatic regulation implemented during REM sleep may be initiated by ripples and spindles during preceding nREM sleep", it is interesting to notice that the selective inhibition of GABAergic neurons of the medial septum, said to be the source of theta rhythm during REM sleep led to spatial and contextual memory impairment (Boyce et al., 2016). In this view, and since hippocampal firing changes during REM sleep are correlated with spindles and SRWs occurrence during SWS, it raises the possibility that depending on how relevant an event is (Wilhelm et al., 2011; Oudiette et al., 2013), this event would be transferred from hippocampus to neocortical areas in its "rough" shape, while its specific components (emotional, contextual and spatial) would be consolidated and integrated during REM sleep.

4.3.2 - Findings in humans

Due to understandable methodological constraints, human studies that investigated traces of memory replay in humans have focused their attention on less invasive designs such as fMRI and positron emission tomography (PET) scans. In this view, numerous studies have provided results showing an increase of brain activation during subsequent sleep (Maquet et al., 2000; Peigneux et al., 2004; Bergmann et al., 2012). In one of these, the results did not only show a hippocampal reactivation after sleep but also a correlation between post-sleep performance and the magnitude of the reactivation (Peigneux et al., 2004). Human studies provided evidence that replay during sleep could enhance memory formation, although it must be admitted that brain imaging studies tend to suffer from low temporal resolution (Kim et al., 1997; Ravi and Goodyear, 2001), impeding characterization of memory replay and its mechanisms (Schreiner and Staudigl, 2020). EEG studies however, can provide strong

time resolution. Nevertheless, they are strongly limited by their poor spatial resolution and the depth of the signal recording, at least for the classic surface EEG devices. These limitations have been resorbed using intracranial EEG (iEEG) recording (Zhang et al., 2018; Jiang et al., 2019; Jiang et al., 2020; Creery et al., 2022). The classic paradigms used with iEEG are visual-spatial memory tasks where participants were instructed to learn sequences of pictures (Zhang and al., 2018) or place them correctly in a grid (Creery et al., 2022). Among the main findings, an increase of gamma range (30-90 Hz) in the medial temporal regions, correlated with the performance, has been often raised (Zhang et al., 2018; Creery et al., 2022). Although iEEG study provided breakthrough in terms of EEG neural markers of memory replay, their major limitations come from their poor sample size range, from 5 participants (Creery et al., 2022) to 20 in the best scenario (Jiang et al., 2019; Jiang et al., 2020), which poses the issue of the lack of statistical power and thus the question of the reproducibility. The second main limitation is about the clinical content of the studies. Indeed, the individuals enrolled in the iEEG are epileptic patients (Zhang et al., 2018; Jiang et al., 2019; Jiang et al., 2020; Creery et al., 2022). As the epilepsy can be described as a maladaptive neural plasticity (Scharfman, 2002) and as the hippocampal seizures are the most common expression, biased EEG signal during recording in these regions cannot be completely excluded.

4.3.3 - Promoting reactivation during sleep: emergence of TMR

As mentioned earlier, numerous findings provided insightful elements about the importance of neural replay as the representation of reactivation of networks previously involved during encoding and reinforced during sleep, leading to the progressive long-term integration of memory (**for review, see Sara, 2010**). On that basis, a promising technique known as "Targeted Memory Reactivation" (TMR) was proposed and applied to reproduce the spontaneous neural reactivation and consequently enhance sleep-related benefits. Although a TMR protocol may vary in terms of cueing stimuli and material to consolidate, it always comprises of three steps (**Figure 11**): (1) Encoding of sensory-cued materials that can be olfactory (Rasch et al., 2007), or auditory (Rudoy et al., 2009; Tamminen et al., 2017; Goldi and Rasch,

2019) during wakefulness. (2) During sleep, the same cue is presented to induce spontaneous reactivation of the neurons engaged during encoding. (3) Recall accuracy is assessed by comparing the cued and non-cued materials.

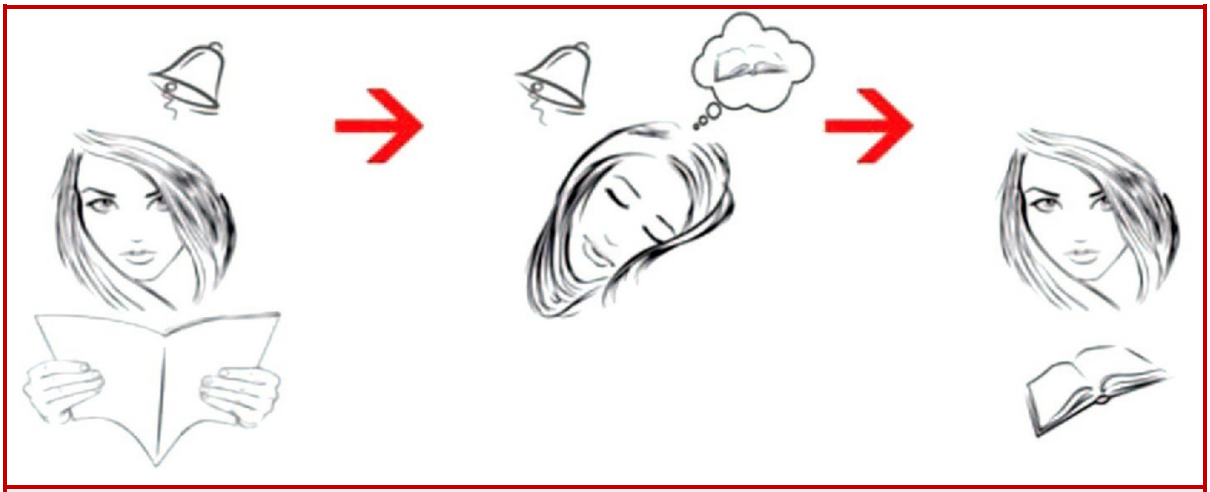


Figure 11: Schema representing the main concept of the TMR. Firstly, a material is learnt and associated with a specific cue (odour, tactile stimulation, or sound). Secondly, the stimulus is replayed, resulting in a reactivation of the material learnt before sleep, and the strengthening of the neuro networks involved.
(Source: Paller, Ken. (2018). Do House-Elves Clean Your Brain While You Sleep?. Frontiers for Young Minds. 6).

TMR has been mostly used in protocols that assessed memory consolidation (Fuentemilla et al., 2013; Sterpenich et al., 2014; Cairney et al., 2018; Goldi et al., 2019). However, this method has also been applied for grammatical generalization (Batterink and Paller, 2017), language acquisition (Batterink et al., 2017; ss al., 2018), classical music (Gao et al., 2020), procedural (Cousins et al., 2014; Rakowska et al., 2021) or emotional memories (Cairney et al., 2014; Pereira et al., 2023).

4.3.3.1 - Application of TMR during SWS

While cueing during sleep was already applied since the early 1950s (Fox and Robbin, 1952), it wasn't until the early 2000s that research on TMR experienced significant growth. This increase of interest was notably marked by two influential studies (Rasch et al., 2007; Rudoy et al., 2009) which provided robust behavioural evidence of the benefits of TMR during SWS. In Rasch et al.'s study, participants have been tested

with an object-location memory task associated with the exposure to an olfactory stimulus, specifically the odour of a rose. Following re-exposure to this odour during SWS, a notable enhancement in memory was observed, especially when the odour was presented during both the learning phase and SWS. Interestingly, TMR application of odour only during learning or when the exposure during learning did not precede a sleep phase was shown to act as a distractor, leading to an impairment of memory. In hindsight, olfactory cues offer advantages: firstly, it is less disruptive to sleep compared to auditory cues (Carskadon and Herz, 2004), and secondly, it directly involves the medial lateral cortex, a pivotal region for associating sensory elements with events and their integration within the hippocampus, particularly with regards to odours (Zelano and Sobel, 2005; Herz, 2016). However, despite this study offered compelling evidence for the benefits of TMR in memory retention, the choice of an olfactory cue may also raise concerns about its specificity, namely its potential to only trigger contextual memory related to the task. This apprehension was addressed in a subsequent study (Rudoy et al., 2009) that also used an object-location memory task. In this study, some items were associated with semantically related sounds, such as a "meow" sound linked to a picture of a cat. Following a 75-minute nap, the post-sleep assessment revealed a significantly lower error rate for the cued items compared to the uncued condition. However, a concern arising here is the duration of sleep, in a sense that participants only experienced a nap rather than a full night's sleep. This factor can impact the number of SWS and REM sleep cycles, which are presumed to contribute to memory consolidation (Batterink et al., 2017).

The exploration into the neural mechanisms underlying the benefits of TMR on memory consolidation has been tackled within the realm of imaging research (Berkers et al., 2018; Shanahan et al., 2018). In an analysis of data derived from Rudoy et al.'s work (as mentioned earlier), one study revealed interesting findings: the visual cortex displayed activity akin to that observed during the initial learning phase (Berkers et al., 2018). Notably, this activation was associated with an increased connectivity with crucial brain regions such as the hippocampus, parahippocampal gyrus, thalamus, and medial prefrontal cortex, all known for their roles in memory consolidation (as previously mentioned). In a separate investigation using an object-location memory

task alongside simultaneous EEG-fMRI recording, another study found a robust and positive correlation between the reactivation of the fusiform gyrus and the ventromedial prefrontal cortex (vmPFC) with recall accuracy (Shanahan et al., 2018). As mentioned earlier, the vmPFC plays a critical role in memory consolidation. Moreover, the reactivation of the fusiform gyrus is in line with its known implication in visual recognition processes, particularly regarding facial recognition.

While most studies applying TMR during SWS have shown positive effects, some have reported negative impacts, ranging from a lack of effect (Wilhelm et al., 2020; Beijamini et al., 2021) to significant disruptions in consolidation (Simon et al., 2018). Ineffectiveness in applying TMR has been observed across various materials or tasks, including problem-solving (Beijamini et al., 2021), word (Wilhelm et al., 2020), or object consolidation (Simon et al., 2018). For instance, in the case of problem-solving (Beijamini et al., 2021), the study aimed to determine if TMR could enhance completion of a video game and whether its effects were influenced by the sleep stage during which the stimulation occurred (SWS, REM sleep, or wakefulness). While most participants with a period of offline sleep displayed significantly improved game completion compared to those in the wake offline condition, the difference disappeared when TMR was applied. Interestingly, the ability to complete the game became equivalent between wake and sleep conditions, irrespective of the sleep stage. Surprisingly, it seemed that only the wake condition benefited from TMR, a conclusion diverging from Rasch's findings about TMR and wakefulness (Rasch et al., 2007). This discrepancy might be related to the concept of prior knowledge, a notion that will be detailed later (**cf. infra, chap. 4.3.4 – Factors of influence**). Wilhelm's study, highlighting the persistent lack of TMR effect even after a week, raises two primary concerns. Firstly, the participants were aged between 11 and 13 years old, potentially introducing biases such as circadian desynchronization due to social life and physiological changes, especially in brain areas like the frontal and prefrontal regions that continue maturing until the late 20s. Secondly, TMR was applied during nREM sleep without distinguishing between stage 2 or SWS, raising the question about the potential lack of specificity in the stimulation process. While inconsistent findings in

the TMR field might stem from various factors (such as human factors, material types,

statistical variability), the discussion about the participant's prior level of knowledge before TMR (Cairney et al., 2016; Groch et al., 2017) and the specificity of the stimulation process (Goldi et al., 2019; Santamaria et al., 2022; Wang et al., 2022) will be delved into later as these factors could play a crucial role in determining the efficiency of TMR (**cf. infra, chap. 4.3.4 – Factors of influence**).

4.3.3.2 - Application of TMR during REM sleep

Traces of TMR application during REM sleep are notably scarcer compared to studies focusing on SWS, although not entirely absent. The main reason about the difference between the presence of TMR during SWS and during REM sleep in research lies in the challenges of precisely applying TMR (**cf. infra, chap. 4.3.4 – Factors of influence**) and executing it during the early morning hours when REM sleep is most prevalent, all without disturbing the participants' sleep by waking them up. Lastly, it is reasonable to lie the absence of studies in REM sleep by the numerous unsuccessful results that emerged. Indeed, this field of research is mainly represented by unsuccessful results from emotional memory (Sterpenich et al., 2014; Rihm and Rasch, 2015; Lehmann et al., 2016) or procedural skills (Laventure et al., 2016; Koopman et al., 2020b). However, there is an exception in the study of emotional memory and TMR during REM sleep that revealed positive findings (Sterpenich et al., 2014). In this study, participants underwent fMRI while encoding a series of faces associated with specific emotional valences (neutral or negative). Half of these pictures were cued with sounds, and TMR was administered during REM sleep or stage 2 of sleep. The post-sleep assessment revealed that participants exhibited higher accuracy when TMR was applied during REM sleep compared to stage 2 sleep or compared to a control condition without sounds. Functionally, a positive correlation was observed between accuracy and medial temporal activation among the group exposed to TMR during REM sleep.

4.3.3.3 - Application of TMR in the specific case of transitive inference

As previously discussed, reactivation during sleep is not only presented as a key mechanism used to foster memory consolidation but also to facilitate the integration and restructuring of both old and new memories, contributing to schema restructuring and enriched representations. This restructuring is thought to aid individuals in employing Transitive Inference (TI), enabling them to infer and solve problems based on given premises. In the field of TMR and memory research, only a recent paper aimed to explore whether TMR during Slow-Wave Sleep (SWS) could enhance TI ability (Santamaria et al., 2022; preprint version). This study is remarkable by the way the TMR was applied at a high level of specificity. Indeed, while the studies commented in the previous sections barely attempted to distinguish TMR application during REM versus SWS, Santamaria' study investigated whether TMR application during up-phase versus down-phase of SO could lead to specific effects. Such a choice of specificity is supported by the fact that SO up-phase are known to drive the thalamo-cortical spindles, known to play a role in the reactivation (Rasch and Born, 2013). The second reason comes from close-loop TMR studies that exhibit stronger evidence of TMR benefits when applied during up-phase, compared to the down-phase (Shimizu et al., 2018; Goldi et al., 2019). Finally, this study also differs by its analysis of long-term sleep benefits after 2 weeks, instead of 12 hours or a couple a day of delay. The paradigm is a classic TI task where the participants had to learn 3 lists of items comprising of faces, objects or scenes. After they were tested, they went to sleep and brain activity was recorded by EEG. TMR was applied during the up-phase, or the down-phase, whereas the last series of item did not receive TMR. Finally, the participants were tested immediately after sleep and two weeks later. At the behavioural level, the results from the session after sleep revealed a significant and higher accuracy for the inference pairs in the UP condition, compared to the control or down-phase condition. Moreover, TMR benefits were shown to persist after two weeks.

4.3.4 - Factors of influence

Like many fields of research, results from TMR and memory have yielded conflicting outcomes, revealing positive impact (Santamaria et al., 2022), lack of effect (Wilhelm et al., 2020; Beijamini et al., 2021), or complete disruption of consolidation (Simon et al., 2018). As raised in the previous section, the recent results from Santamaria et al. highlighted how TMR benefits might rely on the specificity of methodology applied for its application (Santamaria et al., 2022). At the electrophysiological level, recent studies have raised the possibility that TMR benefits might depend on the phase of stimulation during SWS (Goldi et al., 2019; Santamaria et al., 2022). In a recent study, Goldi and al. aimed to investigate whether TMR applied during SO up-state or down-state could improve the consolidation of declarative memory in a classic word-pair task paradigm (Goldi et al., 2019). Interestingly, they also aimed to understand how the percentage of REM sleep spent could modulate the interaction between the phase of stimulation and the TMR effect. At the behavioural level, the results exhibited contrasting findings as no difference was shown between the up-state or down-state stimulation. However, a significant difference was found between the control condition (without stimulations) and the up-state cueing one only. Surprisingly, the results also revealed a negative correlation between the accuracy and the time spent in REM sleep, excepted for the down-state cueing condition. At the electrophysiological level, the up-state condition revealed a higher and significant difference in the theta and spindles band between the remembered and non-remembered words. This finding is partially in line with Santamaria an al. results that revealed a difference in the spindles band for the up-phase stimulation, and a difference between down versus up in the theta band. However, no difference was shown in the down-state cueing condition, raising the possibility that TMR applied during SO down-state phase may disrupt the theta and spindles activities, two frequency bands that were shown to promote memory consolidation, as mentioned earlier. Finally, the contrast between up and down-state conditions for the remembered words revealed a significant and higher spindle activity for the up-state one. As a conclusion, if the main results support the assumption whereby the phase of stimulation may play a crucial role in TMR efficiency, the interesting finding about REM sleep's modulatory effect raises the question of its

role in the consolidation. One the one hand, REM sleep has been found to play a role in declarative memory consolidation (Grosmark et al., 2012; Boyce et al., 2016; Miyawaki and Diba, 2016). On the other hand, SO during SWS have been shown to promote the hippocampal-neocortical transfer of memory.

Building on it, it is reasonable to posit that down-state TMR application might have a disruptive effect on the transfer of memory due to alteration of spindles during SO but not on the consolidation process that occur during REM sleep. However, due to the spindle's disruption, this consolidation would take place in the hippocampus instead of the neocortex. Further replications are needed to clarify the role of the phase stimulation upon TMR related-benefits (short term versus long term consolidation, brain areas involved…). Among the factors assumed to modulate TMR benefits, the level of prior knowledge before its application has recently been investigated (Cairney et al., 2016; Groch et al., 2017). In their research, Cairney et al. aimed to investigate whether being active during learning could impact TMR benefits, and whether those benefits may depend on prior knowledge before sleep. After they were trained in a picture location task with cueing sounds, the participant went to sleep for a nap. TMR was subsequently applied during SWS. Post-sleep results revealed a strong and significant difference between TMR and no-TMR, but only for the participants that exhibited a low-accuracy prior sleep. Interestingly, the TMR benefit for the low-encoding group was shown to be mediated by the time spent in SWS. The findings from Cairney et al. study was not only confirmed by the same type of tasks (Creery et al., 2015; Tambini et al., 2017) but also by designs based on motor tasks (Koopman et al., 2020b). Intuitively and statistically, increase of TMR benefits with poor-prior knowledge can be explained by the fact that an already high performance would lead to a ceiling effect, without enough leeway for improvement. Hence, applying TMR would result in an absence of significant benefits. However, the potential positive relationship between poor prior knowledge and TMR benefits poses a dilemma. Indeed, while a weak encoding before sleep might maximize TMR benefits, it might also result in an increased memory decay at long-term. Indeed, Ebbinghaus' findings (Ebbinghaus, 1885) and its recent replication (Murre and Dros, 2015) revealed that

weaker encoding associated with less repetition was associated with a higher probability of memory loss. Building on this, further investigations are crucial to find the best trade-off between an encoding rate that could benefit from TMR effect on the one hand, and lead to a long-term consolidation on the other hand.

5 - Problematic

Although it still remains reasonable to declare that the reason why individuals spend a third of their life sleeping is unclear, decades of research have proven that sleep is not a uniform and stand-by mode stage, but instead, consists of specific stages characterized by specific brain activities. At the cognitive level, the research field about sleep's role in memory have brought compelling evidence about a strong relationship between sleep and various types of memories. More specifically, recent findings managed to go beyond the classic and dichotomic question about sleep's role in memory forgetting or consolidation, to propose a novel approach supported by the concept of memory integration. Based on the key concept of reactivation, sleep has been shown by studies in animals and humans, to play a crucial role in the integration of events and their reorganization. At the electrophysiological level, the concept of reactivation has been illustrated by specific and highly synchronized brain patterns, that have been shown to promote memory integration, especially during SWS, although it appears more and more undeniable that REM sleep and SWS both play a complementary role in memory formation. Recently, a promising technique that aimed to foster memory reactivation known has TMR has pushed the research boundaries. By associating cueing stimuli like sounds, odour or touch, with a specific material to learn and re-presenting it during sleep, the TMR has promoted the usual and biased selective sleep deprivation phasing-out, leading to successful memory boosting. However, the tantalizing advances in the field of sleep research should not trump the lack of knowledge that still remains. Indeed, sleep benefits as well as TMR-related benefits in transitive inference are still unclear. Moreover, little is known about the electrophysiological neural correlates susceptible to explain these benefits. Further investigations are also needed to understand the phase-lock dependence of TMR

during SWS. Finally, the question about the evolution of sleep and TMR-related benefits upon transitive inference as well as the potential changes of neural correlates over time has not yet been solved.

6 - Research objectives

The overall objective of the present thesis is to deepen understanding of how sleep influences transitive inference abilities and how TMR can enhance this effect. A secondary goal is to explore the neural mechanisms underlying transitive inference during SWS and REM sleep, particularly examining brain frequencies and their interactions in relation to transitive inference-related brain regions. Additionally, this thesis aims to investigate the effects of TMR on cognitive flexibility by replicating laboratory conditions in a real-life setting through a home-based experimental design.

Chapter 2 will assess the progression of sleep-related benefits on transitive inference in a remote study where testing sessions occur 12 hours and one week after learning. Participants in the wake group will be trained in the morning and tested on the same day in the evening, while those in the sleep condition will be trained in the evening and tested the following morning to prevent potential biases from sleep deprivation.
In **chapter 3**, the focus will be on applying TMR during REM sleep using a remote home-based device to examine its effects on transitive inference. This section will involve short-term (12 hours after training) and long-term (one week after training) testing sessions. An analysis of theta and gamma coupling, known for aiding memory integration during REM sleep, will be conducted to explore the neural underpinnings of transitive inference during this sleep stage. Due to the COVID-19 pandemic restrictions, both the experimental designs in Chapters 2 and 3 will be conducted remotely.
Lastly, **chapter 4** will feature a TMR study conducted in laboratory conditions, primarily focusing on SWS-related benefits through targeted stimulation during slow oscillations (SOs). This study will delve into delta and spindle dynamics as well as delta and gamma frequency coupling to assess their potential as neural correlates of

transitive inference. Phase-preference investigation will also be conducted to gain insight into the mechanisms underlying TMR benefits. These investigations will consider the time lapse between encoding and transitive inference testing, examining short-term (12 hours after sleep) and long-term effects (one week after sleep).

Chapter 2: SLEEP BENEFITS DRIVEN BY COGNITIVE FUNCTIONS? COMPARATIVE ANALYSIS BETWEEN CONSOLIDATION AND TRANSITIVE INFERENCE

Abstract

Decades of research have provided strong evidence about the positive sleep influence on numerous cognitive processes, especially memory consolidation. Recently, it has been posited that sleep could also play a role in relational memory, a type of memory that could result from the reorganization of episodes, which in turn could promote new associations between memories, and thus, foster rule guessing or the occurrence of adaptive strategies to solve issues. Building on these assumptions, transitive inference, or the ability to deduce a relational statement (AC) based on shared similarities between premises (AB and BC) has recently been assumed to be improved by sleep. However, little is known about this relationship. The present study aimed to further knowledge about sleep's role in consolidation and relational memory but also about the long-term persistence of these potential benefits. For that purpose, participants were enrolled in a transitive inference (TI) protocol comprising of a consolidation and transitive inference testing sessions. Overall, main findings revealed that a full night of sleep after learning was associated with a positive effect on accuracy for both recall and TI accuracy. Moreover, a protective effect from memory decay between testing 12 hours after learning and testing at follow-up after a week was observed but only for the recall accuracy, namely the consolidation component. Taken together, the present findings suggest that whether sleep could contribute to the formation and integration of memory is not a forgone conclusion but may depend on the cognitive process engaged in specific situations. Building on these positive behavioural results, further research is needed to understand the cognitive factors and functions behind the positive relationship between sleep and relational memory.

1 - Introduction

Decades of research have established a global consensus regarding the positive effects of sleep on the consolidation and enhancement of declarative memory (Marshall and Born, 2007; Diekelmann and Born, 2010; Born and Wilhelm, 2012; Rasch and Born, 2013). Although the exact mechanisms behind the strengthening of memory traces and the facilitation of their retrieval and recall, reported in numerous sleep studies (Gais et al., 2002; Huber et al. 2004; Girardeau et al., 2009; Mölle and Born, 2009; Sara, 2017; Cairney et al., 2018) still remain unclear, recent research has provided elements about a mutual contribution from slow-wave sleep (SWS) and rapid-eye movement (REM) sleep that would be respectively involved in the abstraction of gists or hidden rules, leading to the formation of semantic schemas or representations, and the restructuration of shared semantic representation between new and old memory traces, leading to the formation of new memories (Lewis and Durrant, 2011; Lewis et al., 2018). Described by two complementary cognitive models, namely the "information overlap to abstract" (iOTA) and "broader form of the information overlap to abstract" (BiOtA) frameworks, memory traces would be progressively integrated following a two-steps process. (1) Overlapping memories replayed in the neocortex and controlled by the hippocampus would be submitted to Hebbian plasticity, leading to the extraction of similarities between events replayed close together in time. Although memory decay may affect traces recently encoded because of synaptic downscaling (Tononi and Cirelli, 2006) or long-term depotentiation (Poe et al., 2000), overlapping similarities between some of these may remain. (2) Semantic similarities between events that are replayed during REM sleep by the cortex and triggered by ponto-geniculo-occipital waves would be detected and restructured with novel associations to create new memories and knowledge. Interestingly, it has been posited that the process of transformation and reorganization of memory traces would be the starting point of relational memory building, a cognitive function that supports abilities to guess hidden rules (Sio et al., 2013; Wagner et al., 2004) or use adaptive strategies (Beijamini et al., 2014; Lewis et al., 2018).

In the field of relational memory, transitive inference (TI) represents a complex cognitive function that involves deducing a relational statement (A>C) based on shared similarities between premises (A>B and B>C). For instance, one can infer that "smoking kills (AC)" by recognizing that smoking habits (A) increase the risk of developing heart disease and lung cancer (B), which in turn increase the risk of death (C). The association between sleep and TI is evaluated through a standardized three-step paradigm. A series of items (pictures of objects, faces, landscapes...) hierarchically ordered (e.g., A > B > C > D > E) is split by pairs of adjacent items (A > B; C > D...) called premise pairs. The participants are instructed to (1) learn the relationship between items within the pairs by trial-error reinforcement but without being informed about the hierarchy. During the night (2), sleep promote inference by creating new chains of associations between items (AC, BD, DE…). After sleep (3), the participants are tested on these new associations of pairs (inference pairs) to assess sleep's role in TI. Such type of paradigm was tested in a seminal study that found a significant difference in TI ability between sleep and wake groups, 12 hours after the learning session (Ellenbogen et al., 2007). Interestingly, the sleep group was shown to exhibit a higher accuracy as distance between pairs increased, but only after 24 hours of retention. Importantly, not only cognitive research but also the clinical field has shown sleep benefits on TI and a correlation with a reduction of age-related memory decline (Golkashani et al., 2021).

However, numerous studies were shown to exhibit an absence of benefits from sleep upon cognitive flexibility were challenged by numerous contradictory findings (Morgan and Stickgold, 2017; Talamini et al., 2022). In a study that aimed to compare sleep versus incubation effects on riddles, visual change detection and anagrams did not find any sleep benefits regardless of the task (Brodt et al., 2018). Only a positive incubation effect was found for riddles tasks. Similarly, a study that compared sleep versus incubation benefits on magic tricks and insight problems (Schönauer et al., 2018) did not find significant difference between sleep wake benefits. An interesting study that aimed to compare sleep versus wake benefits on case of murder solving through a video-game, for which participants were tested on multiple criteria such as reasonableness, consistency, story recall, fluency, flexibility, originality and elaboration

skills (Hołda et al., 2020) did not provide any sleep benefits, regardless of the criteria assessed.

Several studies that aimed to address the questions about sleep and relational memory reported that task difficulty may drive TI ability, with greater benefits from sleep observed as the task became more challenging (Sio et al., 2013). At the cognitive level, monitoring associated with the presence of feedback and reinforcement at learning has been shown to promote TI and increase sleep benefits (Werchan and Gomez, 2013). Furthermore, metacognitive skills, such as awareness of the hierarchical structure and the implementation of strategic approaches during the learning process, have been identified as drivers of sleep-related benefits (Martin and Alsop, 2004; Lazareva and Wasserman, 2009). Moreover, and based upon Ellenbogen's findings regarding delayed sleep benefits on TI accuracy (Ellenbogen et al., 2007), time between learning and testing was shown to play a crucial role to reveal sleep benefits. Indeed, in a recent study (Cousins et al., 2021), participants were trained to memorize factual knowledge, followed by a period of offline retention of either 12 hours of sleep or wakefulness. Subsequently, participants were tested on their retained knowledge immediately after the offline period, after 2 hours, and after 1 week. Interestingly, only the testing session after 1 week revealed a significant benefit for the sleep group, indicating that the advantages of sleep on TI may take time to occur.

Building on these observations, the overall objective of this experiment was to further knowledge about the potential modulatory effect of sleep upon transitive inference and at lower scale, upon memory consolidation by comparing premise pairs accuracy between sleep and wake groups. Moreover, the second objective was to challenge the question of the interaction between sleep and time required to observe potential benefits. Concretely, the study aimed to compare how a full night of sleep could promote transitive inference compared to a similar period of wake and finally, evaluate the evolution of sleep benefit after a week. Using a classic TI paradigm that comprised of 2 sets of fictive objects, faces and landscapes, the main hypothesis posited that after a full night of sleep, the participant could exhibit a higher accuracy for the

premise pairs, but also for the inference pairs. Finally, a protective effect from memory decay was expected after a week, illustrated by a less negative evolution rate (ER).

2 - Methods

2.1 - Participants

Forty-two healthy students (20 F and 22 M) aged between 18 and 30 (26 ± 3) were recruited in the study via social networks. None of them had sleep disorders (measured by the Insomnia Severity Index - ISI) (Morin, 1993), visual or hearing problems. The anamnestic data analysis confirmed that the participants did not suffer from clinical anxiety or depression (evaluated with the Hospital Anxiety and Depression Scale - HADa and HADd) (Zigmond and Snaith, 1983). The experiment was approved by the Cardiff University Internal Review Board and all participants gave written informed consent before participation (No. EC.20.01.14.5935R2A).

2.2 - Presentation of the items

The material consisted of a set of 9 black and white faces, objects or scenes (Horst and Hout, 2016) (**for example of stimuli, see Supplementary section S1, cf. infra**). Each item was given a rank to create 3 blocs made of 3 faces, 3 objects and 3 landscapes, hierarchically arranged (e.g., item A > item B >...n) (**Figure 1a**). Each block was used to build 8 premise pairs (PP) and 28 inference pairs (IT) (**Figure 1d**).

2.3 - Experimental procedure

Participants were split into two conditions; sleep or wake, and completed three sessions (**Figure 1e**): (1) a learning-session before sleep where participants were trained on premise pairs, (2) a testing session 12 hours following sleep or wake to test them on the premise and inference pairs and (3) a follow-up seven days after to assess long-term memory changes across time. The experiment was designed with Psychopy© and conducted online with Pavlovia©. Each session was performed

remotely. Although the participants were instructed to run all the tasks autonomously, they were given the possibility to contact by chat the experimenters while they performed. Moreover, each task was preceded by a practice session. The sleep group started session 1 between 8 and 10 p.m. and session 2 between 8 and 10 a.m. after 12 hours of sleep whereas the wake group started session 1 between 8 and 10 a.m. and session 2 between 8 and 10 p.m. after 12 hours of wake. Finally, participants were asked to perform each session in a quiet room. For visibility and practical purpose, mobile phones were not allowed for training and testing sessions.

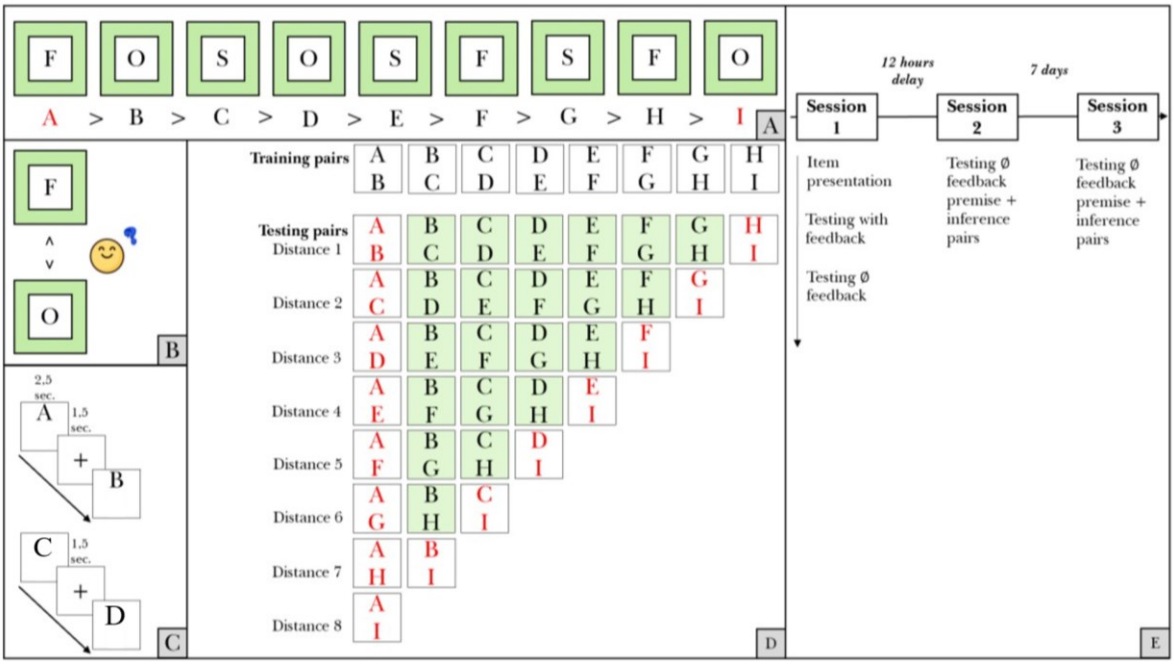


FIGURE 1 (**a**) Schematic representation of a series of items. F, O and S respectively stand for "faces", "objects" and "scenes". The red items (A and I) are called "anchors" items and were removed from the final data analysis. (**b**) Schematic representation of a trial. The presentation of each item is always vertical and the participant is instructed to press UP or DOWN key to select which item is supposed to "cover" a happy smiley. (**c**) Detailed representation of a training session during the session 1. (**d**) Presentation of the premise and inference pairs. Probe pairs with a green background were used for data analysis whereas the red ones (anchors) were excluded as the first and last pairs are respectively always dominant or submissive. (**e**) Schematic representation of the experimental design.
Figure adapted from Jensen and al., 2019 (Figure 1)

Before the training session started, a series of item was created for each participant (**Figure 1a**). The creation was pseudo randomized to avoid overlapping between types of items (e.g., Object Scene Face Scene Face Object but not O.S.**F.F**.O.S). Given the fact that there is 6 ways to choose the initial position of face, object, scene, and

for each pattern, 3! (factorial 3 = 3*2*1) to arrange each face, object and scene position, the number of different sets given was 6^4 = 1296 sets, ensuring a different set for each participant.

The first session started with a learning procedure where each item was presented for 2.5 seconds and followed by a fixation cross for 1.5 sec. (**Figure 1c**). Precisely, the participants were shown a white background screen with a series of instructions in black color: "TRAINING SESSION: a series of pictures will appear in the screen one by one", "please watch the sequence and try to remember as many pictures as possible". The instructions were followed by the message "GET READY" in red and a countdown of 3 seconds. Building on the series created, the nine items were presented one by one, each item separated by a red fixation cross for 1.5sec. The participants were instructed to watch the sequence carefully and try to remember the items.

After the presentation, the participants were informed that a series of items previously presented would be displayed by pair. An example of a pair was displayed vertically with one item at the top and a second one below. The two items were separated by a picture of "UP KEY" arrow below the item on top, and a "DOWN KEY" arrow on top of the second item (**Figure 1b**). On the right, a picture of a happy yellow smiley and a blue question mark were displayed. The participants were given the instruction to press "UP" or "DOWN" key to choose and guess which item could be associated with the happy smiley. They were also informed that first trials would be pure guessing but by trial-error reinforcement, the task would become easier. The reason of the presence of the smiley and the instructions given served the purpose of making participants learning the hierarchy among the premise pairs without being aware of it. Again, each pair was presented in a pseudo-randomized order to avoid overlapping type of adjacent pairs (e.g., a face followed by another face). The participants were informed about the fact that for each trial, they would receive the correction that would take the shape of the pair previously displayed and a green square around the correct item for 3 seconds. After each answer, the participants were given a preliminary negative or positive feedback. Precisely, after a trial, the pair and the happy smiley disappeared. Then, a positive response led to a big yellow happy face smiley whereas a negative

one revealed a red angry smiley. The feedback was followed by the presentation of the pair and the correct response, irrespective of the correctness of participants' response. Finally, the participants were also informed about the fact that a minimum accuracy was expected to pass the test (without knowing the percentage) or a certain number of set trials.

The first testing session stopped after participants reached at least 80% of accuracy twice in a row or after 10 sets of trials. After 5 min of distracting typing task, the testing session without feedback started (**Figure 1e**). Similarly to the previous session, the participants were informed and instructed to find the correct association between a specific item from the pair they were previously presented and the smiley. Concretely, this session was similar to the first one excepted the absence of feedback and the order of presentation. The session ended after participants reached 80% accuracy twice in a row, or after 10 sets of trials. After session 1, the sleep and wake group were respectively allowed to go to bed or to go back to their daily routine.

Session 2 started after 12 hours of wake (from 8-10 AM where testing session 1 ended to 8-10 PM the same day) or after 12 hours that contained a full night of sleep (from 8-10 PM where testing session 1 ended to 8-10 AM the next day) (**Figure 1e**) depending on the group condition. Again, similar instructions were given. The main difference however, was the presence of inference pairs. More precisely, participants were tested on their ability to recall the premise pairs learnt before, but also on new indirect inferential item associations (**Figure 1d**) varying in distance degree, for a total of 8 premise and 28 inference pairs presented in normal and reversed order (e.g., AB; BA for the premise pairs or BD; DB for the inference pairs). The testing phase was repeated 3 times, always with a different pair ordering. For experimental purpose, the participants were not informed about the presence of new pairs associations (inference pairs).

A week after session 2, participants were asked to repeat the same sequence. For this session 3, the pairs presented were similar but displayed in a different order.

2.4 - Data analysis

In order to prevent bias resulting from ceiling effects and to account for variability among participants, the global average across trials was used, even though each participant achieved the required 80% accuracy threshold to pass Session 1. Concretely, using the accuracy from the last set of trial would result in a ceiling effect as all the participants reached at least 80% of accuracy, thus leading to a narrow range of variability. In order to avoid it and since a participant that reaches 80% of accuracy twice in a row after 2 sets of trials differs in terms of encoding strength from another that would reach 80% but after 10 sets of trials, the overall mean between all sets of trials was used to take that difference into account.

Additionally, in the analysis, anchor pairs were excluded, and only probe pairs were considered for calculating accuracy. Anchor pairs, which consist of the first or last item in the hierarchy, were omitted because they tend to be easier to remember due to their consistent dominance or submissiveness.

The data analysis was preceded by a computational detection of features of interest. This process aimed to extract useful information from large data sets and avoid noisy features. The computational approach was a wrapper method, where a global model was calculated and trained based on the features from the dataset. Depending on their ability to explain the variance of the computed model, the features are saved or removed from the model by backward elimination. For that purpose, the method BORUTA was chosen (**see Prabhakaran, 2017 for detailed explanations about BORUTA application with Rstudio**). BORUTA is a feature selection algorithm used in machine learning to identify the most important features for a given model. It operates by iteratively comparing the importance of real features with that of random features (shadows). This approach is based on the concept of random forest, which aims to capture the important features that can explain a particular outcome. The algorithm consists of two steps:
(**1**) The dataset is duplicated and a random forest classifier is trained to detect the important features by assigning a score for the mean decrease in impurity for each

feature. A high score is associated with high importance. Three categories are formed. The "shadow min" includes the features with a low importance score, the "shadow mean" includes the features that are close to chance. Finally, the "shadow max" includes the features with high importance.
(**2**) The algorithm compares the importance of the duplicated features with that of the real dataset. After a certain number of iterations, a real feature is retained if it has a higher z-score than its shadow.

The importance score for each feature in the BORUTA analysis is derived from the importance measure provided by a random forest model. Random forest models, in turn, provide importance scores for each feature based on how much they improve the model's performance when they are included. A positive importance score indicates that the feature contributes positively to the predictive performance of the model. The higher the score, the more important the feature is deemed to be. A negative importance score implies that the feature detracts from the model's performance. This might seem counterintuitive, but it can occur for several reasons:
1/ The feature might be adding noise to the model, reducing its accuracy.
2/ The feature could be correlated with other features (multicollinearity), leading to unstable importance scores.
3/ The feature might interact poorly with other features (interaction effect) in a way that negatively impacts the model's overall performance.

The parsimony and the quality of the models were assessed with the Mallow Cp (**see Bobbitt, 2021 for detailed explanations about Mallow Cp calculation with Rstudio**), a variant of AIC (Akaike Information Criteria) developed by Colin Mallows. Technically, the likelihood of a given model can be increased by adding more parameters. Thus, the more parameters used, the more informative the model. However, because the coefficient used (R^2) is a square, it cannot decrease as more parameters are added, which can improve the explanatory power of a model due to chance rather than the efficiency of its parameters. To limit this bias, the Mallow Cp was applied to assess the fit of the regression models on the basis of the features detected by BORUTA. The main objective here was to detect the most precise and

accurate model that would need the lowest number of predictors to reach that precision. Among multiple models available, the one that exhibits the lowest Cp value is the most precise. Mallow Cp is calculated as follows:

Mallow Cp = (SSE_p / MSE_F) - (N - 2P)

. SSE_p = Sum of square errors for the potential model
. MSE_F= Mean square error of the full model
. P = number of predictors. The penalty N-2P represents the cost for a model that incorporate high number of predictors.

This method is consistent with the concept of parsimony, which aims to find a trade-off between the explanatory power of a model and its ease of use.

The magnitude of the difference between means was described by using the Hedge's g. This effect size is the non-biased equivalent of the Cohen's d but for small sample size (n < 50). The formula used to calculate Hedge's g was:

Hedge g = (M1 - M2/ SD pooled) * (N - 3 / N - 2.25) * ((√N - 2) / N)

. M1 - M2 represent the mean difference.
. SD pooled is the weighted standard deviation

Finally, the adjusted R^2 was used as a coefficient of determination (**see Bobbitt, 2020 for detailed explanations about adjusted R^2 calculation with Rstudio**). This coefficient is consistent with the use of the AIC, as it captures the degree of parsimony of the model used. Technically, a malus is added to the R^2 if a predictor improves the model by less than chance. This process aims to avoid a natural increase in the R^2 value when predictors are added to the model, since the coefficient cannot decrease (a square is always positive). However, the penalty is reduced if a predictor is found to increase model accuracy more than by chance. The adjusted version of the R^2 is always lower than its biased version.

The formula is presented as follows:

Adjusted R^2 = 1 - (1 - R^2) (N - 1) / N - p - 1

. N = sample size
. p = number of predictors

3 - Results

As described earlier in the Methods section, the participants were trained on three sets of items, namely faces, objects, and landscapes. The objective behind this decision was to investigate the potential impact of item type on the relationship between sleep and cognitive processes such as consolidation and transitive inference. However, a preliminary analysis revealed that there was no significant effect of item type ($F(2, 123) = 1.392$, $p = 0.103$). Therefore, based on these findings, the accuracy data from each type of item were combined and averaged together.

3.1 - Feature detection

To ensure the experimental integrity of the study but also given the time period of data collection during the COVID-19 pandemic, several anamnestic factors were controlled. Factors such as chronic insomnia, clinical depression, and anxiety were accounted for to prevent any impairment of participants' abilities during the tasks. Anamnestic and experimental features were transformed into predictive factors to assess premise and inference accuracy. The BORUTA feature detection process included seven anamnestic (e.g., age, sex, ISI) and experimental (time, condition) features that could explain the variations in premise and inference accuracy among participants as follows:

. Age of the participants
. Gender (Male or Female)
. ISI, a self-screening questionnaire score that aims to assess the severity of insomnia
. HAD.a, a self-screening questionnaire score that aims to assess the severity of anxiety
. HAD.d, a self-screening questionnaire score that aims to assess the severity of depression
. Condition (sleep group versus wake group)
. Time (Session 1 / 2 and 3 for the premise and Session 2 / 3 for the inference pairs).

For both premise and inference accuracy, the maximum number of iterations was 400 to ensure a trade-off between complete attribution and time- processing. The results revealed that all the features were attributed (to drop versus to keep) before the

program reached the maximum number of iterations.

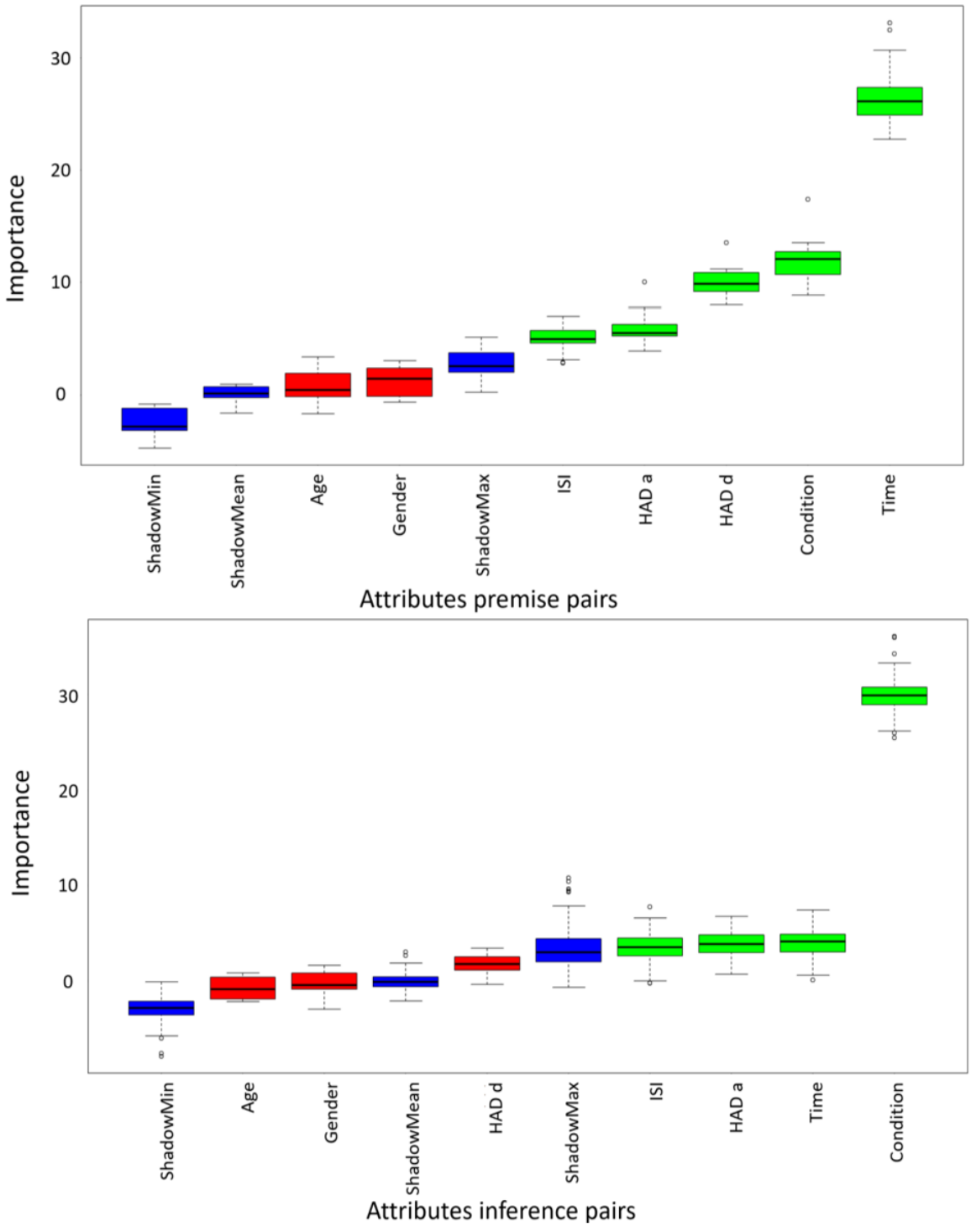


Figure 2: Representation of the features of interest for premise and inference pairs, sorted by degree of importance. (**a**) Premise pairs accuracy is mostly explained by the time feature. Each feature of interest is strongly higher than randomness effect represented by the shadows (blue boxplots) (**b**) The same features for the inference pairs accuracy were found but after 312 iterations, which is explained by the small difference between features selected and the max shadow effect.

For the premise part, the BORUTA analysis stopped after 17 iterations and identified five features of interest (ISI, HAD.a, HAD.d, condition, time), which exhibited significantly higher Mean Decrease Accuracy (MDA) than the shadows (representing randomness). Two features (age, gender) had higher MDA than the average shadow effect but did not exceed the maximum randomness effect, so they were dropped from further analysis (**Figure 2a**). The same procedure was applied to the inference part (**Figure 2b**), where three features (age, gender, HAD a) were rejected, and four features (ISI, HAD a, condition, time) were considered as features of interest. Notably, compared to the 17 iterations in the premise part, the inference part required 312 iterations, which was close to the maximum limit. This is reflected in the MDA exhibited by the features of interest, which were nearly equivalent to the MDA from the maximum shadow effect, except for the "condition" feature.

Building on BORUTA analysis, both premise and inference accuracy were found to be influenced by anamnestic factors like the ISI and HAD scores. It cannot be excluded that the sanitary context may have increased the already well-known effect of insomnia and anxiety upon cognitive skills, especially memory consolidation. More importantly, and although both condition and time features appeared to play a crucial role on premise and inference accuracy, it is interesting to notice that time appeared to be the main source of explanation of the variation of premise pairs accuracy, whereas the transitive inference accuracy was mostly explained by the sleep versus wake condition. Finally, and building on the main objective of the present study, the features “Condition” and “Time” were selected to create the future combinations of models susceptible to explain the accuracy for the premise and inference pairs.

3.2 - Comparative analysis of model’s accuracy and parsimony

Building on the detection features of interest from BORUTA, the selected features were used to compare different parsimonious models susceptible to explain the accuracy with a high explanatory power and degree of generalization. Concretely, a series of combinations between the selected features found with BORUTA was performed to detect which one could predict in a best way the variability of accuracy

for both premise and inference pairs.

For that purpose, the function ols_step_all_possible from the Rstudio package Olsrr was used to compute and test all possible combinations of features susceptible to build a statistical model. For each model, the rank, the predictors included, the R^2, Adj. R^2 and Mallow's Cp were given. Given the main objective of the study that consisted in evaluating sleep's role upon premise and inference abilities, the model "premise pairs accuracy ~ condition" was chosen as the baseline model for the premise pairs and "inference pairs accuracy ~ condition" for the inference pairs condition. As a precision, the sign (~) can be defined as "explained by". Finally, the best model among the combinations was extracted and compared to the baseline (**Figure 3**).

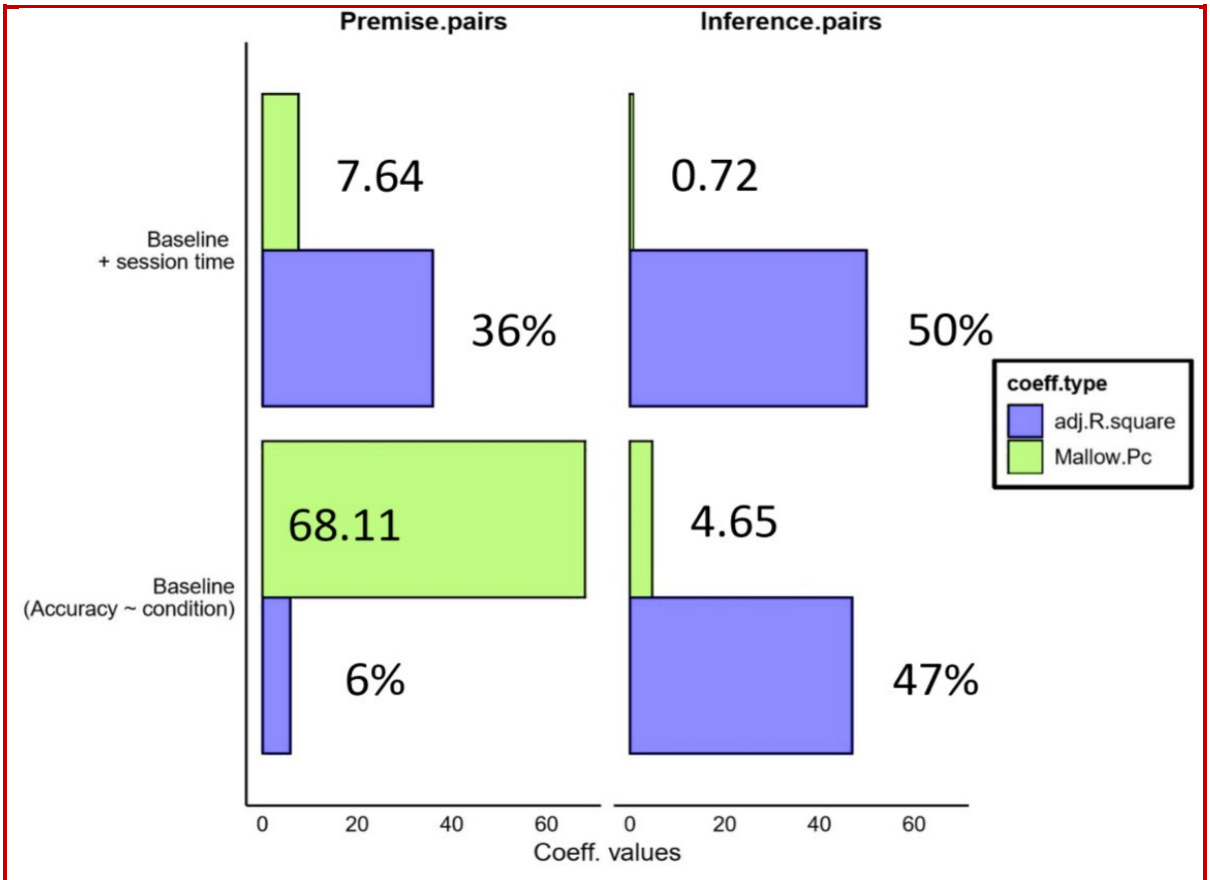


Figure 3: Representation of the comparisons between the baseline and the most parsimonious model for premise and inference pairs. For each model, the adj. R^2 and Mallow's Cp were extracted and compared. A combination between a small Mallow's Cp value and a high adj. R^2 coefficient is associated with a highly parsimonious and accurate model.

For the premise pairs, the following model was assessed:

Premise pairs accuracy ~ condition + HAD a + HAD d + ISI + time

namely, how premise pairs accuracy variability can be explained by the experimental condition, and/or the degree of anxiety…Gender feature was excluded because the unequal proportion between males and females and the age because of irrelevancy. Indeed, because of the narrow range (from 18 to 30 years old) of values, this feature was considered as not relevant for any deeper analysis. On that basis, 31 different combinations were proposed. The most parsimonious and unbiased model extracted contained the condition (sleep/wake) and the time (Session 2 and Session 3) as regressors. Compared with the baseline, the Adj. R^2 and Mallow's Cp appeared significantly greater (baseline Adj. R^2 = 0.06, model Adj. R^2 = 0.36; baseline Mallow's Cp = 68.11, model Mallow's Cp = 7.64). The strong and significant difference between the model chosen and the baseline was confirmed by the F test (F(, 124) = 29.857, p = 2.788e-11).

For the inference pairs, the following model based on BORUTA feature detection was assessed:

Inference pairs accuracy ~ condition + HAD a + ISI + time

Based on the number of regressors, 15 different combinations were proposed. Here again, the model that integrated both time and condition appeared to be the most parsimonious and unbiased model. However, the comparison of the coefficients revealed similarities between the models (baseline Adj. R^2 = 0.47, model Adj. R^2 = 0.50; baseline Mallow's Cp = 4.65, model Mallow's Cp = 0.72), excepted for the Mallow's Cp, 6.5 times higher for the baseline (**Figure 3**). Consequently, and although an Adj. R^2 almost similar, the F test revealed a significant difference between the two models (F(, 82) = 6.101, p = 0.0156).

In conclusion and despite of different trends between premise and inference pairs accuracy, the anamnestic factors that appeared as good candidates were dropped from the final model building. In comparison, the interaction between experimental condition (sleep/wake) and session time (12 hours after learning/ 7 days after learning) appeared to be the most parsimonious predictors of accuracy.

3.3 - Increase of memory consolidation after sleep

To assess the relationship between sleep and memory, the absolute means and evolution rates were compared over time between the learning phase and both testing and follow-up session. Contrary to many studies assessing relational memory, the statistical analysis was performed on both premise and inference pairs to investigate about potential changes in sleep benefits according to whether the cognitive process involves recall for premise pairs, or transitive inference for inference pairs.

Data from the baseline revealed that sleep and wake groups reached the same performance (**Figure 4**).

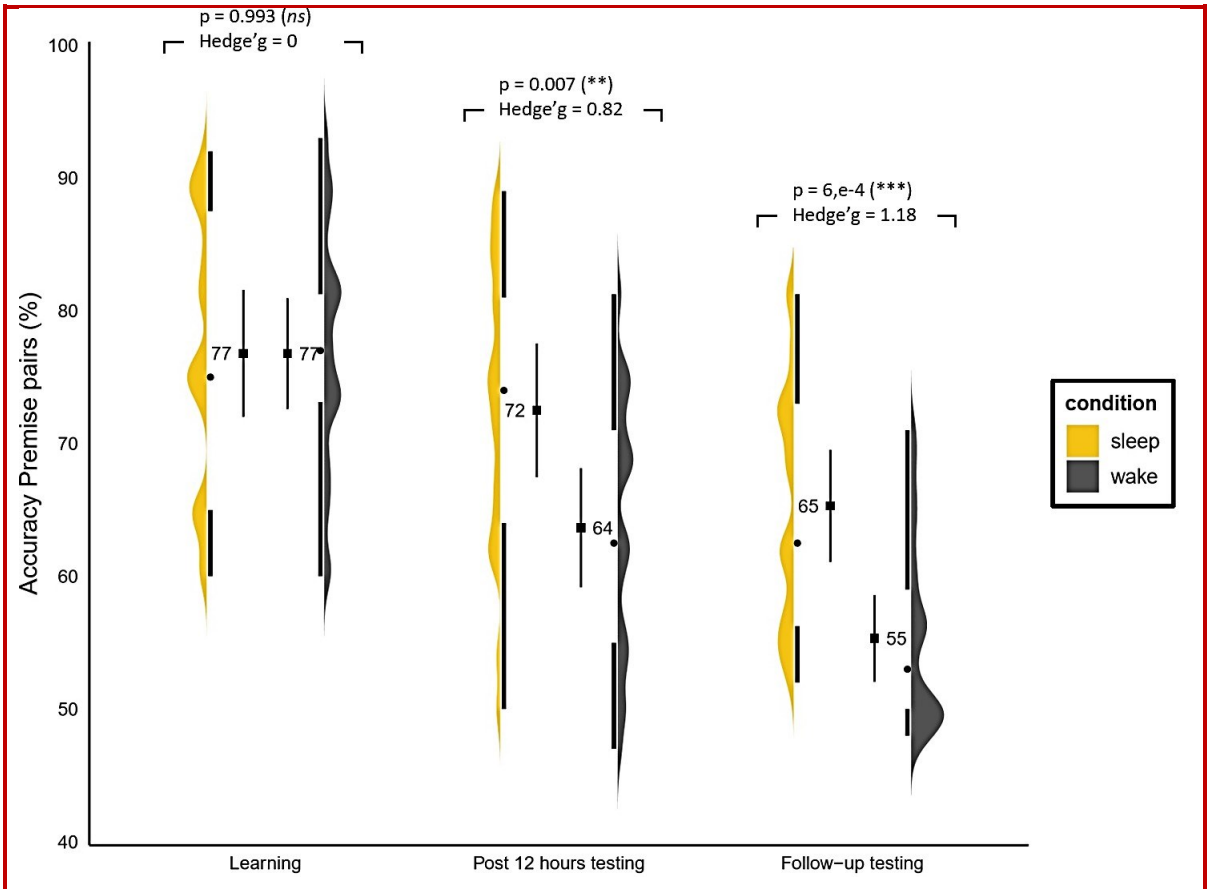


Figure 4: Accuracy for the premise pairs at learning, testing after 12 hours and after 7 days (N = 21 participants per groups, 42 per session). Dots and thick black lines are minimalist boxplot representations. Black squares and numbers are means and error bars are CI. ns = non-significant.

Moreover, each group exhibited a decrease of accuracy after 12 hours of retention. However, a significant and strong protective effect was found across time for the sleep

group. Changes in sleep benefits over time was quantified by a 2*3 ANOVA (sleep/wake and Session 1, 2 and 3) that revealed a significant effect of the condition in favour of sleep ($F(1, 82) = 13.526$, $p = 0.0003$), as well as a significant session time effect ($F(2, 123) = 31.028$, $p = 1.38e-11$) and finally, a significant interaction between both features ($F(2, 123) = 3.392$, $p = 0.036$). Post-hoc comparison between sleep versus wake conditions revealed a significant protective effect of sleep ($t(62) = 4.09$, $p = 0.0001$, 95% CI [2.109, 10.45]; Hedge's g = 0.527, 95% CI [0.88, 0.171] Table 1). In the short-term, the steep fall observed in the wake group (-16.88% of accuracy) was offset by a strong protective sleep effect in the sleep group (-6.49% of accuracy). The difference of evolutive direction is reflected by a significant difference between sleep and wake at session 2 ($t(20) = 3.00$, $p = 0.007$, 95% CI [2.312, 15.38]; Hedge's g = 0.828, 95% CI [0.191, 1.466] **Figure 4**).

At long-term level, the same trend was observed between session 2 and 3 seven days after. Although a slight reduction gap was observed, the changing dynamics between session 2 and 3 for the sleep group exhibited a much lesser negative rate (-9.72%) compared to the wake group (-14.06%). Again, a significant difference of absolute mean between the two groups was noticed ($t(20) = 9.976$, $p = 0.0006$, 95% CI [4.793, 15.16]; Hedge's g = 1.18, 95% CI [0.517, 1.843]) (**Figure 4**). Given the group differences found between sleep and wake, it can be reasonably admitted that sleep benefits on memory consolidation is reliable. Moreover, such a benefit, that took the form of a protective effect, tended to preserve memory against decline over the long-term. A summary of the main findings is presented Table 1 (**cf. infra**).

3.4 - Sleep rather than wake promotes transitive inference

As analyzed above, sleep versus wake benefits in transitive inference abilities were assessed by comparing the absolute means within sessions and the evolution rates between testing and follow-up sessions. Moreover, a regression analysis was performed between the accuracy at learning and the accuracy at testing after sleep or wake to assess whether pre-sleep or wake state could predict inference abilities.

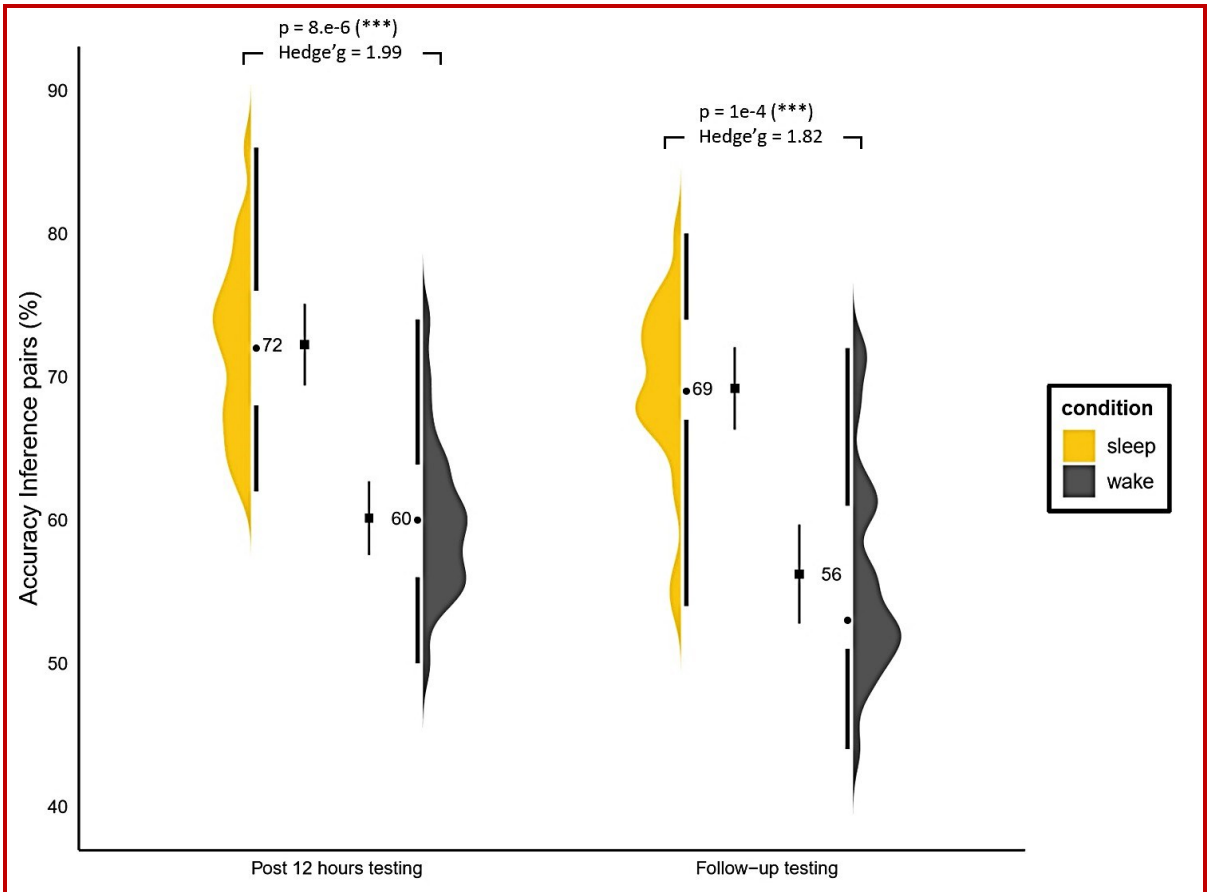


Figure 5: Accuracy for the inference pairs after 12 hours and after 7 days (N = 21 participants per groups, 42 per session). Dots and thick back lines are minimalist boxplot representations. Black squares and numbers are means and error bars are CI. ns = non-significant.

Overall, the results revealed a significant relationship between premise pair accuracy at learning and inference abilities after 12 hours of incubation for the sleep group (adj.R^2 = 0.172, p = 0.047) but not the wake group (adj.R^2 = 0.002, p = 0.775) (**Figure 5**).

Knowing that both groups exhibited an equivalent performance at learning (77% of accuracy each), the difference between regression results cannot be explained by any difference in encoding or at bigger scale, a forgetting curve that could be more pronounced for one group. Hence, and despite of a quite small effect size (17.2%), it can be reasonably accepted that this preliminary result provides evidence of sleep's role in relational memory. In line with these findings the 2*2 ANOVA (sleep/wake and Session 2, 3) revealed a strong effect of condition (F(1, 82) = 78.432, p = 1.68e-13) and session-time (F(1, 82) = 6.033, p = 0.0162) but no interactions. The comparison of accuracy at testing revealed a significant difference between the sleep and wake

groups (t(20) = 5.94, p = 8.25e-6, 95% CI [1.393, 7.82]; Hedge's g = 1.99, 95% CI [1.246, 2.744] **Figure 5**). The same significant trend appeared at follow-up testing (t(20) = 4.71, p = 0.0001, 95% CI [2.805, 7.32]; Hedge's g = 1.82, 95% CI [1.094, 2.55] **Figure 5**). Interestingly, the evolution rate between session 2 and 3 for both groups exhibited a slight decrease but without any significant changing dynamics between sessions (-4.16% for sleep group and -6.66% for wake group). Compared with the trend from the premise pairs that revealed a steep fall for the wake group but not for the sleep group, it can be assumed that the nature of sleep benefits may vary depending on the type of memory process engaged. The main findings about sleep's role in transitive inference are presented Table 2 (**cf. infra**).

3.5 - Main findings about sleep benefits in this experiment

The main objective through the comparison between sleep's influence in memory retrieval for premise pairs and transitive inference for the inference pairs was to determine whether the type of pairs could have an impact on the level and the nature of that influence. More precisely, a ceiling effect at encoding stage was created to analyze how sleep could on the one hand, promote memory recall and/or transitive inference and on the other hand, how sleep could preserve these benefits against decline across a long-time period (seven days).

Table 1 | Sleep's role on premise pairs accuracy

	Statistical results	
Factors (ANOVA)	p-value	Hedge g
Session	$1.38e^{-11}$	-
Condition	0.0003	-
Session * condition	0.036	-
Condition (t-test)		
Sleep versus wake	0.0001	0.527
Session (t-test Holms)		
Learning 1 vs Testing	$5.54e^{-8}$	0.818
Testing vs follow-up	$2.58e^{-7}$	0.734
Interaction (t-test Holms)		
Sleep vs Wake - Learning	0.993	0.002
Sleep vs Wake - Testing	0.007	0.828
Sleep vs Wake - Follow-up	0.0006	1.18

Overall, premise pair accuracy revealed that sleep not only fostered recall but also tended to preserve it across time against memory decline. Indeed, wake after encoding lead to a lower level of accuracy after 12 hours but also to a massive decrease across time (-22% after a week) compared to sleep (-12%). In comparison, transitive inference accuracy revealed a slightly different influence of sleep. Although all the participants performed above chance, sleep after encoding leaded to a much higher accuracy (72%) compared to wake (60%).

Table 2 | Sleep's role on inference pairs accuracy

	Statistical results	
Factors (ANOVA)	p-value	Hedge g
Session	$1.68e^{-13}$	-
Condition	0.0162	-
Condition (t-test)		
Sleep versus wake	$4.4e^{-9}$	1.86
Session (t-test Holms)		
Testing vs follow-up	0.0004	0.38
Interaction (t-test Holms)		
Sleep vs Wake - Testing	$8.01e^{-6}$	1.99
Sleep vs Wake - Follow-up	$1.02e^{-4}$	1.82

However, whether wake or sleep followed encoding did not influence the level of preservation against decline across time. Indeed, despite a decrease of accuracy more pronounced for the wake group compared to sleep, the difference of evolution rate after a week appeared to vary by only 2.5%.

As a conclusion, it can be assumed that if sleep benefits in global memory abilities is constant irrespective of the type of memory, whether sleep plays a role in the preservation against decline across time strongly varies with the type of memory and the cognitive component engaged in the process of memory transformation or consolidation.

3.6 - Classification of sleep's role in consolidation and inference

Building on the findings that revealed a significant effect of condition (sleep versus

wake) and time (Session 1 versus Session 2 versus Session 3) for the premise and inference pairs, the present section aimed to determine to what extent the results were due to chance. For that purpose, a binary logistic classification has been applied. Through the analysis of premise pair accuracy, the objective was to evaluate potential sleep benefits upon memory consolidation process at short and long-term. At short-term, the evolution rate ((Final value – Initial value) / Initial value) between learning and testing after 12 hours was used as a predictor to test the probability of belonging to the sleep or wake group. The same procedure but between session 2 and 3 was applied to test the long-term evolution. Finally, the potential benefits of sleep for transitive inference skills were evaluated at short and long-term. The short-term period was evaluated by using the absolute mean value at session 2 as a predictor of the probability to belong to the sleep or wake group. The long-term evolution was evaluated by using the evolution rate between session 2 and 3.

3.6.1 - Sleep benefits upon consolidation at short and long-term

The relationship between sleep and short-term consolidation was evaluated via the following model: glm(condition ~consolidation.r, family=binomial(link = "logit"). Condition output referred to the group "sleep" and "wake" and the predictor "consolidation.r" to the evolution rate between learning and immediate testing after 12 hours of sleep or wake. 60% of the data was extracted to train the model. The testing upon the 40% of remaining data revealed a strong level of corrected (accuracy = 0.76) and a good capacity to discriminate between classes (AUC =0.78, 95% CI [0.65, 0.93]. The result revealed a significant association between the binary output and the predictor (p = 0.007) (**Figure 6a**). Concretely, the logistic regression identified that higher level of consolidation rate was associated with a higher probability of sleep occurrence between learning and testing (OR = 1.22, 95% CI [1.04, 1.56].

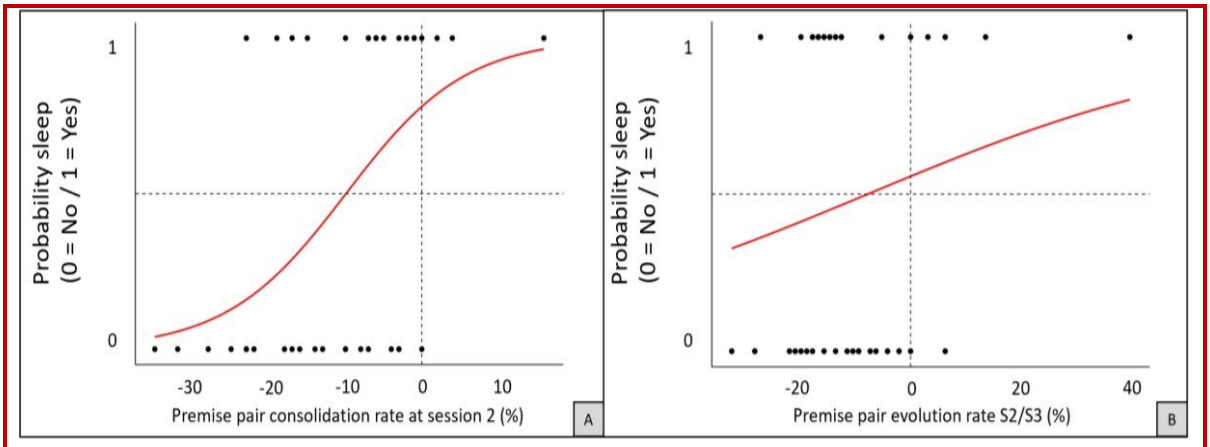


Figure 6: Logistic relationship between the consolidation rate at session 2 as a predictor of sleep versus wake. (**a**) The probability of sleep occurrence versus wake is predicted by the consolidation rate ((testing - learning) / learning) at testing session for the premise pairs. (**b**) Sleep occurrence is predicted by the evolution rate of consolidation across the week. Vertical black dashed line represents a null consolidation rate, namely the absence of difference of accuracy between testing at learning and testing at session 2. Horizontal black dashed line represents a probability of 50% of chance, or the random effect. A flat trend from the red line is associated with random effect whereas a sigmoid curve represents a high model accuracy.

The same procedure was applied for the long-term consolidation. Here, the model used was glm(condition ~long.term.r, family=binomial(link = "logit"). Condition output still referred to the group "sleep" and "wake" and the predictor "long.term.r" to the evolution rate between testing 12 hours after learning and the follow-up session that occurred 7 days after. After being trained on 60% of the data, the testing upon the 40% of remaining data points revealed poor accuracy (accuracy = 0.52) as well as a low and volatile capacity to discriminate between classes (AUC =0.57, 95% CI [0.36, 0.71], close to randomness. The inaccuracy of the model is illustrated by the non-significant association between the binary output and the predictor (p = 0.242) (**Figure 6b**). Here, a higher level of consolidation rate did not appear to be modulated by the probability of sleep after learning (OR = 1.04, 95% CI [0.98, 1.15].

As a conclusion, and in line with the well-established positive relationship between sleep and memory consolidation, testing 12 hours after learning has pointed out the strong modulatory effect of sleep upon consolidation process. However, and despite a significant and strong effect size observed after comparing sleep versus wake at follow-up testing (**Figure 4**), the same trend has not been observed while performing logistic classification, raising the possibility that long-term benefit from sleep might be due to chance. The main findings are presented Table 3 (**cf. infra**).

3.6.2 - About sleep's role in transitive inference at short and long-term

The following analysis aimed to evaluate how higher level of inference accuracy could predict the sleep onset probability at short and long-term. The first relationship between short-term inference accuracy and sleep was built on the following model: glm(condition ~inference.r, family=binomial(link = "logit"). The "condition" output illustrate the binary probability (sleep versus wake) and "inference.r" the absolute mean of inference accuracy 12 hours after learning. Here, the model was trained by extracting 60% of the data. The 40% of remaining data was used to test the model, which appeared to exhibit an excellent positive rate (accuracy = 0.81) associate with a capacity to discriminate between classes that almost reached perfection (AUC =0.91, 95% CI [0.81, 1]. The main findings revealed a significant association between the binary output and the predictor (p = 0.0166) (**Figure 7a**). Precisely, the logistic regression identified that higher level of inference rate was associated with a higher probability of sleep onset between learning and testing (OR = 1.32, 95% CI [1.11, 1.77].

Finally, the binary classification was also applied at long-term. The model used comprised of the following parameters: glm(condition ~long.term.r, family=binomial(link = "logit"). Condition output referred to the group "sleep" and "wake" and the predictor "long.term.r" to the evolution rate between testing 12 hours after learning and the follow-up session that occurred 7 days after.

The model was also trained on 60% of the data and tested on the 40% that remained. In line with the findings about long-term sleep benefits upon consolidation, the model appeared to reveal a level of correctness particularly poor (accuracy = 0.42) lower than chance, but interestingly associated with a decent ability to discriminate between classes (AUC =0.62, 95% CI [0.45, 0.79].

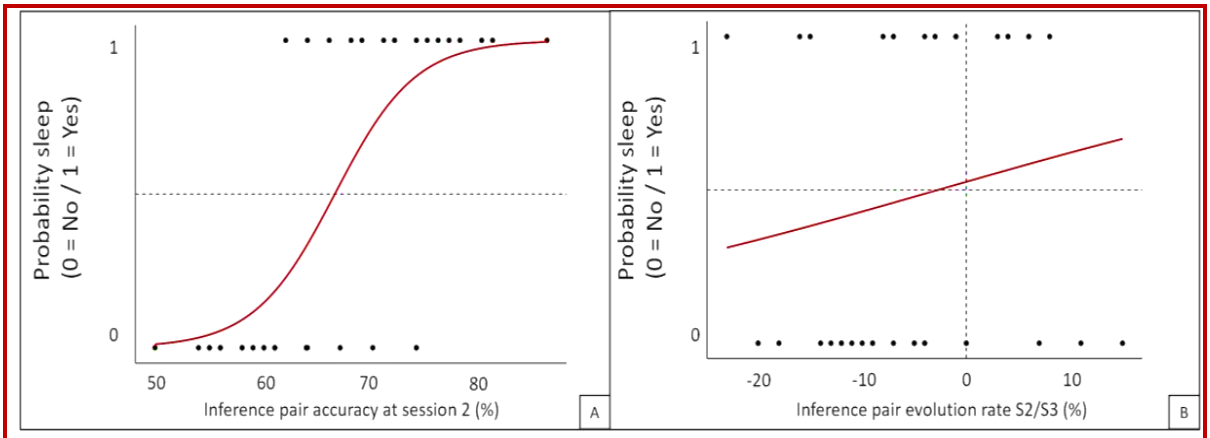


Figure 7: Logistic relationship between the inference accuracy at session 2 as a predictor of sleep versus wake. (**a**) The probability of sleep occurrence versus wake is predicted by the accuracy at testing session for the inference pairs. (**b**) Sleep occurrence is predicted by the evolution rate of consolidation across the week. Vertical black dashed line represents a null consolidation rate, namely the absence of difference of accuracy between testing at learning and testing at session 2. Horizontal black dashed line represents a probability of 50% of chance, or the random effect. A flat trend from the red line is associated with random effect whereas a sigmoid curve represents a high model accuracy.

The difference between accuracy and AUC can be easily explained by the fact that the model is able to discriminate between positives and negatives but not true or false values, which indicates a high level of bias. Finally, and unsurprisingly, the inaccuracy of the model is illustrated by the non- significant association between the binary output and the predictor ($p = 0.825$) (**Figure 7b**). The logistic classification revealed that higher level of inference accuracy 7 days after learning did not depend on sleep onset after learning (OR = 1.01, 95% CI [0.89, 1.14].

As a summary, the findings from the logistic classification revealed that inference accuracy similarly to consolidation, appeared to predict with a high level of precision, whether the participants slept before testing, but only at short-term. The trend is in line with the behavioural comparison (**Figure 5**) for which the evolution rate between testing and follow-up appeared to be particularly low. The main findings are presented Table 3 (**cf. infra**).

Table 3 | Binary classification of accuracy and sleep onset probability

		Statistical results			
Output	Predictor	p-value	Odd ratio	Accuracy	AUC
Premise pairs accuracy					
Sleep vs. wake	ER (12 hours)	0.007	1.22	0.76	0.78
Sleep vs. wake	ER (7 days)	0.242	1.04	0.52	0.57
Inference pairs accuracy					
Sleep vs. wake	μ (12 hours)	0.016	1.32	0.81	0.91
Sleep vs. wake	ER (7 days)	0.825	1.01	0.42	0.62

4 - Discussion

Sleep, an essential physiological process, has long been acknowledged for its significant role in the consolidation of memories and numerous cognitive functions like executive functions or mood. However, the precise mechanisms by which sleep protects against long-term memory decay remain unclear, as does its impact on transitive inference, a specific type of relational memory that involves inferring novel relationships based on associations between existing knowledge. Therefore, the objective of this study was to contribute to existing knowledge by investigating the potential modulatory effect of sleep on transitive inference and memory consolidation at short and long-term intervals.

The study assessed the accuracy of premise pairs and inference ability after a full night of sleep and after one week. Additionally, a binary logistic classification was employed to gather additional information on the potential influence of sleep as a determinant factor in memory consolidation and inference. Consistent with the literature, the findings revealed a significantly higher consolidation rate after sleep compared to wakefulness. Furthermore, sleep onset after learning was associated with reduced long-term memory decay. Evaluation at short-term revealed a similar trend for inference pairs. However, intriguingly, there were no group differences in the rate of evolution between the short and long-term assessments. The logistic classification analysis aligned with the behavioural results, revealed a positive odds ratio and strong model accuracy in the short-term, but only marginal and nonsignificant trends in the long-term, even for the premise pairs, raising questions about the persistence of sleep

benefits over time.

Several limitations of this study should be considered. Firstly, it is important to note that data collection took place during the initial stages of the COVID-19 pandemic, a period characterized by stress and potentially depressive factors related to sanitary measures and the overall context (see "Features of interest" section). Numerous studies have retrospectively highlighted significant impairments in mood, sleep quality, and cognitive functions during the pandemic. Therefore, generalizing the present findings to different contexts should be approached with caution. Secondly, in line with the pandemic context, the study was conducted remotely. Despite providing participants with guidance and requesting them to perform the task in a quiet room, replicating laboratory conditions at home posed challenges, and thus, it cannot be excluded that the participants' accuracy may have suffered from sources of disturbance. Another limitation pertains to the lack of physiological markers for memory consolidation and transitive inference. Due to the remote nature of the study, no EEG recordings were included. Consequently, despite the significant and robust results, the behavioural findings lack support from EEG markers like spectral, time frequency markers or cross-frequency coupling analysis. Finally, the small sample size may have impacted the classification. While 21 participants per group is typically sufficient to detect significant behavioural trends, logistic regressions requires splitting the dataset, using 80% for model training and 20% for testing. In this study, a 60% threshold was chosen, potentially leading to pitfalls due to insufficient training data and limited testing data. These limitations, though not exhaustive, should be taken into account in future studies.

In conclusion, both memory consolidation and transitive inference abilities appear to be strongly dependent on the onset of sleep following learning. However, future studies seeking to enhance understanding of long-term effects and applications in home settings should consider incorporating supervised technologies in their protocols. These technologies could include remote EEG tools, simple training programs that offer guidance on improving sleep hygiene based on participants' sleep disturbance reports, sleep monitoring to identify optimal sleep phase onset, and

assistance in managing mood disorders. Advancing knowledge of why the saying "to sleep on it" holds true could have implications in various fields, such as professional environments that require creativity or teaching methods based on self-monitoring.

5 - Supplements

S1: Representation of a sample from the pictures used during the experiment. Objects from the database were selected because of their imaginary shape. The faces and landscapes were selected for their neutral content, reinforced by the white and grey colors.

Chapter 3: TARGETED MEMORY REACTIVATION DURING REM SLEEP: THETA-GAMMA COUPLING AS A BIOMARKER OF TRANSITIVE INFERENCE

Abstract

Sleep has long provided evidence about its crucial role in cognition, especially memory consolidation. Recently, numerous findings have also proven sleep benefits upon its ability to reorganize memory to promote new associations, which in return could play a role in the emergence of inference, adaptive strategies and issue solving. However, the question about which stage could be involved in the process of cognitive flexibility is unclear. According to the BiOTA model, REM sleep would be crucial in this process, promoting the association between old and new memories boundaries. Building on this assumption, the present study aimed to test with a transitive inference task at short and long-term, associated with a TMR stimulation protocol during REM sleep to investigate how it could improve ability to infer. Moreover, a cross-frequency coupling approach based on theta phase and low gamma amplitude was performed to investigate about EEG correlates susceptible to explain TMR benefits. Behaviourally, the main findings revealed a significant effect of TMR during REM on accuracy but only after a week, suggesting that memory remodeling is not an immediate process but requires time. At the EEG level, TMR application during REM was shown to increase the strength of the signal coupling. However, MI did not appear to correlate with transitive inference accuracy. Taken together, these findings provide for encouraging results about sleep's role in cognitive flexibility and TMR mechanisms upon brain signal processing.

1 - Introduction

Decoding environment, often made of relentless stream of various situations and interactions implies the use of stereotypical thinking and generalizations. However, in some situations for which this approach is inaccurate, monitoring processes involving executive functions like planning or inhibition (Miyake et al. 2000) or deeper, flexible and adaptive strategies like heuristics are required.

Among these strategies, transitive inference (TI) is a widely used holistic cognitive function defined by the ability to build new assumptions (AC) or strategies based on premises (AB and BC). As an example, in a situation where (A) "I need to take my car to go to my job interview" tempered by the issue (B) "I might be late due bad traffic" implies (C) "If I arrive late, I will miss this job opportunity", it appears crucial to infer that using a car in this situation (AC) is inaccurate. Due to the multiple expressions of cognitive flexibility like reasoning, inhibition, mental flexibility, or planning, a full comprehension of cognitive flexibility mechanisms appears quite challenging. However, decades of research have brought the hypothesis whereby the insight resulting in the associations between distant premises in TI would be fostered by sleep (Bowden et al., 2005; Luo et Knoblich, 2007; Kumaran, 2013). Represented by the cognitive iOTA and BiOTA models, sleep is assumed to promote the formation of new connections between past and recent events that shares characteristics (Lewis et al., 2018), improvement of issue-solving skills (Sanders et al., 2019), rule comprehension (Batterink et al., 2014) and inferential reasoning (Ellenbogen et al., 2007; Werchan et Gómez, 2013; Behrens et al., 2018; Aly et al., 2021, 2022). However, positive effects from sleep upon cognitive flexibility like transitive inference were challenged by numerous contradictory findings. Indeed, a study that aimed to compare sleep versus incubation effects on riddles, visual change detection and anagrams did not find any sleep benefits regardless of the task (Brodt et al., 2018). Only a positive incubation effect was found for riddles tasks. The same negative findings were sown in a study that compared sleep versus incubation benefits on magic tricks and insight problems (Schönauer et al., 2018). In an interesting study that aimed to compare sleep versus

wake benefits on case of murder solving through a video-game, the participants were tested on multiple criteria such as reasonableness, consistency, story recall, fluency, flexibility, originality and elaboration skills (Hołda et al., 2020). However, the study did not find any sleep benefits, regardless of the criteria assessed.

Separately, the field of research about sleep's role in memory formation has brought numerous findings about memory replay, a key-mechanism of spontaneous reactivation of neural networks engaged during wakefulness emerged (Buzsáki, 1989; Rudoy et al., 2009; Diekelmann and Born, 2010; Paller et al., 2021) that would promote memory consolidation and reorganization. On that basis, a promising technique known as "Targeted Memory Reactivation" (TMR) was proposed and applied to reproduce the spontaneous replay and thus, promote neuronal reactivations and consequently enhance sleep-related benefits. A typical TMR paradigm comprises of three main steps: (1) Encoding of sensory-cued materials, olfactory (Rasch et al., 2007) or more often auditory (Rudoy et al., 2009), during wakefulness. (2) During sleep, the same cue is presented to induce spontaneous reactivation of the neurons engaged during encoding. (3) Recall accuracy is assessed by comparing the cued and non-cued materials.

At the behavioural level, TMR application during REM sleep was shown to significantly improve rule abstraction but only a week after learning (Pereira et al., 2023), which has been described as a potential illustration of "slow form of plasticity". Interestingly, the authors that also applied TMR during SWS did not find any significant effect at short as well as long term. A source of explanation may come from a potential lack of cueing precision since no considerations were taken between cueing at up-phase or down-phase. However, cueing during slow-oscillations up-phase was shown to increase the percentage of spindles and reduce forgetting rate (Ngo and Staresina, 2022). On that basis, a recent study that aimed to further knowledge about the SO up-state versus down-state TMR cueing application during SWS (Santamaria et al., 2023) revealed significant and positive immediate TI benefits after TMR application at SO up-phase, that were shown to persist over two weeks. However, positive effects

from sleep and/or TMR were challenged by numerous contradictory findings. Nevertheless, TMR has not always been found to improve TI (Beijamini et al., 2021). In a study that aimed to compare sleep versus wake benefits in a first experiment and TMR benefits during SWS versus REM sleep versus wake. Main findings revealed a significant sleep benefit compared to wake in issue solving score, but did not find any TMR benefits on issue solving regardless of the sleep stage cued (Beijamini et al., 2021).

Findings from sleep-related benefits upon TI and TMR modulative effects clearly highlight the diverging and unclear content of the relationship between these three components. Moreover, it also appears that furthering knowledge about the EEG dynamics behind sleep and TMR effects is not only a challenging but also a crucial aim to further knowledge about the interaction between the brain regions behind the process of TI. On that basis, the present study aimed to understand the relationship between sleep, TMR and TI. Using a home-based headband (Zmax), this study aimed to evaluate the impact of TMR application during REM sleep on TI ability at both short and long term. As a second objective, this study aimed to further knowledge about the unclear EEG dynamics during REM sleep susceptible to modulate cognitive flexibility required during transitive inference.

REM sleep stage is mostly represented by ponto-geniculo-occipital (PGO) activity (Callaway et al., 1987; Datta and Hobson, 1994) for which their potential contribution in memory formation and synaptic maturation is still debated (Amzica and Steriade, 1996; Li et al., 2017). Moreover, REM sleep is characterized by a complete muscle atonia expected distal twitches (Peever and Fuller, 2016), and body dysregulations like variations of temperatures or heartbeat dysregulation (Siegel, 2005). Although REM sleep's functions are still debated, abnormal PGO-waves patterns have been observed in epilepsy (Frauscher et al., 2018) and Parkinson (Fernández-Mendoza et al., 2009) disease. Finally, REM sleep alteration was shown to be associated with emotional dysregulation (Galbiati et al., 2020). In the field of transitive inference, REM sleep implication and its biomarkers has been poorly investigated. In a study where participants were tested on their ability to detect the tonality of melodies, REM sleep

percentage, in line with a recent study (Pereira et al., 2023) was associated with an increase of schema construction and higher degree of immediate recognition after sleep (Durrant et al., 2015). interestingly, the recognition of tonal melodies (i.e., built upon schemas) was significantly and positively correlated with central and frontal theta activity. REM sleep frontal theta role in issue solving and schema formation has also been supported by a recent study where participants were asked to solve the tower of Hanoi test (van den Berg, 2023). Post-sleep testing revealed a significant difference between the control condition and the one where participants were given the possibility to elaborate strategies in the range of theta and spindle bands.

Studies in humans about REM sleep correlates of memory integration mainly focused on theta activity (Hutchison and Rathore, 2015; Sopp et al., 2017; Pereira et al., 2023; van den Berg, 2023). However, and although studying a single frequency band, like theta alone, might provide information about the involvement of that specific frequency range in a given cognitive process, the coupling between different frequency bands, can offer additional insights into the dynamic coordination and communication between different neural circuits during complex cognitive tasks, thus providing a more nuanced understanding of the interactions between different brain oscillations and offering insights into the complex dynamics of neural processing during various cognitive functions. Over decades of REM sleep research, theta gamma coupling appeared as a reliable biomarker of memory processing, in rodents (Bragin et al., 1995; Lisman, 2005; Colgin et al.,2009; Belluscio et al., 2012; Tort et al., 2013) but also in humans (Canolty et al., 2006; Axmacher et al., 2010; Koster, 2018).

Numerous brain areas are implied in the theta-gamma coupling, namely the medial-temporal regions (Pesaran et al., 2002; Bauer et al., 2007), the entorhinal cortex involved in various cognitive functions, including spatial navigation and memory (Fernández-Ruiz et al., 2021), major interface between the hippocampus and neocortex often referred to as the hippocampal-cortical loop (Neske and Connors, 2016). Theta oscillations were shown to promote associative binding, memory integration between old and recent memories (Clouter et al., 2017) or visual perception (Köster et al., 2017). Gamma oscillations are implied in the promotion of

perception of visual hierarchies (Bosman et al., 2012) and working memory (Kaiser et al., 2003; Daume et al., 2017). Although theta-gamma coupling studies are not common in humans, recent findings about theta-gamma phase-amplitude coupling (PAC) revealed its role in the promotion, maintenance, ordering and binding of information within neuronal networks in the neocortex (Canolty et al., 2006), successful episodic memory encoding (Staudigl, 2013; Heusser et al., 2016) and long-term potentiation (LTP) in hippocampus (Pavlides and al., 1988). Nevertheless, theta-gamma coupling role in the integration of premises and the emergence of TI has never been experimented so far. Furthering the comprehension of REM sleep's implication in memory integration through a reliable neural correlate appears crucial to improve the general knowledge about sleep's role in memory integration.

Building on this, the present study aims to further knowledge about sleep's role in transitive inference emerging at short and long-term and how sleep-related benefits might be modulated by TMR during REM sleep. As a second objective, this study aims to investigate the EEG dynamics following TMR application during REM sleep following encoding, to improve the comprehension about TMR and REM sleep implications in the memory integration and the emergence of TI.

For that purpose, 32 participants were recruited and tested in a transitive inference protocol at short (12 hours after sleep) and long-term (a week after sleep). Since REM sleep benefits were shown to be delayed on time (Pereira et al., 2023), the behavioural hypothesis assumes a higher accuracy after TMR application compared to a control situation but only at long-term. Moreover, the modulation index (MI), main coefficient of coupling strength between a phase and a specific amplitude is assumed to correlated with long-term accuracy. Firstly, at the EEG level, premise learning is assumed to promote the emergence of theta-gamma coupling during REM sleep. Secondly, a higher theta-gamma PAC modulation index is expected after using TMR during REM sleep.

2 - Methods

2.1 - Participants

Thirty-two healthy students (31 females), right-handed and between 18 and 30 (23 ± 2.4) were enrolled in this study. Ten participants were tested in France and 22 in Wales. The experiment was presented in English and dispositions were made to ensure that French participants were fluent enough to understand the instructions and the protocol. Data from four participants were excluded from the final analysis as they did not reach the minimum criteria of accuracy (**cf. infra**). None of them had known sleep disorders (screened by the Insomnia Severity Index) (Morin, 1993), vision or hearing problem. None of the participants was taking any medication at the time of the experiment and none had a history of any neurological or psychiatric disorders. Based on the anamnestic data collection, participants did not report any clinical level of anxiety or depression (screened by the Hospital Anxiety and Depression scale) (Zigmond et Snaith, 1983). The ISI is a self-rated questionnaire that comprises of 7 questions. The score varies from 0 to 28 where higher scores are associated with higher levels of insomnia. For the purpose of this study, the threshold of 14 was chosen as it refers to the subthreshold category of people suffering from insomnia disorder (before the moderate stage). The HAD is also a self-rated questionnaire that comprises of 14 items that range from 0 to 3 for a total of 21. The 14 items are equally divided into 2 sets of questions designed to evaluate anxious or depressive symptoms. For the purpose of the study, participants had to reach a score lower than 7, which refers to the absence of symptomatology. From the day before the experiment to the learning session, the participants were instructed to abstain from caffeine or alcohol. The present study was approved by the internal review board of the University of Cardiff and all the participants gave written informed consent before participating. After completion of the experiment, the participants received a 25£ reward (30€ for the French one).

2.2 - Item and sounds presentation

The items consisted of a series of 6 objects pictures hierarchically ordered (e.g., item A > item B >...n) (**Figure 1a**) leading to the creation of 5 premise pairs (PP) and 10 inference pairs (IP). Precisely, 6 imaginary items were collected from a database (Horst and Hout, 2016) (**for example of stimuli, see Supplementary section S1, cf. infra**). For purpose of neutrality, the background has been removed and the contrast modified so that items only contained grey scales and white colors. On that basis, 6! (factorial 6) sets were created, leading to a potential of 720 sets, ensuring a different series of items for each participant.

The sounds consisted of 3 sounds of 2 seconds used during the learning phase and a shorter version (200 milliseconds) for the TMR. These sounds were selected for their relative semantic proximity with the items (relativeness is justified by the fact that items are imaginary). For example, an object that looked like a dog toy was associated to a squishy sound. Finally, the 3 short sounds (one per targeted item) were pooled together and repeated to create a time series of 9 sounds (3 sounds *3 repetitions) each separated by 2 seconds. The reason is because the Zmax device was not designed to play different sounds. Hence, it has been decided to pull the different sounds to create a unique one that would contain 3 different tones.

2.3 - Stimulation device presentation

The Hynodyne Zmax© is a headband EEG device designed for lucid-dreaming. The central box is secured with a Velcro strap headband that allows multiple head sizes. The box is connected to a 2 biocompatible hydrogel channels set with 4 metallic snaps. The 2 electrodes (F7-Fpz F8-Fpz) are referenced to Fpz. The band width ranges from 0.1 to 128 Hz which theoretically allows a full frequency spectrum recording (from delta waves - 0.1 to 4Hz to gamma waves 30Hz+). The sample rate is set to 256/seconds by default. The device comprises of a 3D accelerometer that can detect head and body movements, captors of temperature and heartbeat. The proprietary algorithm is designed to detect REM sleep episodes but can also provide for sleep

hypnograms with a 30-s epoch resolution differentiating between four sleep stages (N1, N2, N3, REM). The Zmax is connected to the computer program by a Bluetooth connection. The Zmax is provided with a software that allows brain recording, sleep study settings, data saving and EDF data type export.

2.4 - Experimental procedure

Since the study occurred during the pandemic, the study was designed to be performed remotely for safety purpose. As a within subject experiment, the participants were trained and tested with TMR and no TMR items. The study comprised of 3 sessions (**Figure 1e**): (1) a learning- session before sleep where participants were trained on premise pairs, (2) a testing session 12 hours following sleep where they were tested on the inference pairs only and (3) a follow-up seven days after to assess long-term memory changes across time. The tasks were built on Psychopy© and conducted online on Pavlovia©. For sanitary purpose, each session of the experiment was performed remotely with a guidance by chat and/or visuo-call (Zoom©) and practice trials. A full and comprehensive list of instruction was sent to the participants to install the software that would deliver cueing sounds and record brain activity. If needed, a guidance by Zoom© was proposed to confirm that each participant was ready before the task starts. The learning session was scheduled for 9 p.m., and the post-sleep and follow-up testing at 9 to 10 a.m. respectively 12 hours and a week after learning. The participants were asked to perform each session in a quiet room. Similarly to the previous chapter, the participants were instructed to use a computer or laptop to run the different tasks and mobile phones were not allowed.

The first session consisted in learning items, sounds and their association. As for the chapter 2, the participants were instructed to watch carefully the screen as object items were presented one by one for 2.5 sec., each separated by a red fixation cross for 1.5 sec. (**Figure 1c**). The sequence was repeated twice. Similarly, the long version of the sounds was also presented twice, followed by the short version. In a second time, the participants were tested on their ability to associate the sounds and items. For that purpose, the long version of the sound was presented alone, followed by the

associated item and two distractors. The 3 items were presented left, centered and right. For each trial, the participant was instructed to press left, space (centered item) or right key to select the correct association of item and sound without any time limitation. The position of the correct item was randomized for each set of trial. Answered was followed by the correct association represented by a green square surrounding the picture. After the participant reached 100% of accuracy, the task was repeated with the 200ms. sounds without feedback. Again, 100% of accuracy was required.

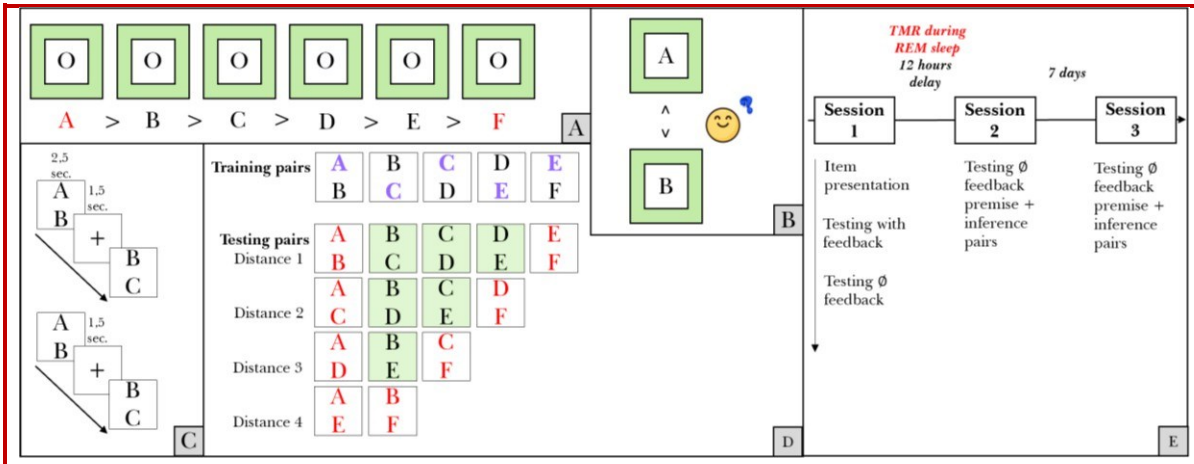


FIGURE 1 (**a**) Schematic representation of a series of items. O letter refers to "objects". The red items (A and F) are called "anchors" items and were removed from the final data analysis. (**b**) Schematic representation of a trial. The presentation of each item is always top/down and the participant is instructed to press UP or DOWN key to select which item is supposed to "cover" a happy smiley. (**c**) Detailed representation of a session period. The top and down sequence respectively represent the training and testing during the session 1. (**d**) Presentation of the premise and inference pairs. Probe pairs with a green background were used for data analysis whereas the red ones (anchors) were excluded as the first and last pairs are respectively always dominant or submissive. The purple letters represent items for which TMR was applied. (**e**) Schematic representation of the experimental design. Each session was performed remotely.
Figure adapted from Jensen and al., 2019 (Figure 1)

Following item/sound association learning task, the participants were trained on the premise pairs. Again, they were informed about the content of the session. Concretely, the series of 6 items was divided into a set of training premise pairs (**Figure 1d**). Each pair was presented centered and vertically, with one item at the top and a second one below. The two items were separated by a picture of "UP KEY" arrow below the item on top, and a "DOWN KEY" arrow on top of the second item (**Figure 1b**). On the right, a picture of a happy yellow smiley and a blue question mark were displayed. The participants were given the instruction to press "UP" or "DOWN" key to choose

and guess which item could be associated with the happy smiley. They were also informed that first trials would be pure guessing but by trial-error reinforcement, the task would become easier. The reason of the presence of the smiley and the instructions given served the purpose of making participants learning the hierarchy among the premise pairs without being aware of it. Each training set contained a top/down pair association of item and the reversed version (e.g., the pair with the item A and B was presented and A at the top and B at the bottom and reversely). Here again, the pairs presentation was pseudo randomized, not to avoid item type overlapping presentation but to ensure that one item could not be followed the second one from the series (e.g., C-B; BC). After each trial and depending on the correctness of the answer given, the participants were given feedback that took the shape of a yellow happy or red angry smiley. After each feedback, the correct response was presented. Importantly, the participants were asked to reach at least 66% of accuracy twice in a row or before 10 sets of trials (**Figure S1**). The reason behind the decision to decrease the accuracy minimum required from 80% to 66% was due to the context of pandemic during which recruitment was particularly challenging and experimental mortality quite frequent. However, in order to consider the degree of variability of encoding between participants (it was assumed here that the strength of encoding between a participant performing correctly twice in a row would be different from another one for which 10 presentations would have been needed to perform correctly), the global averaged accuracy across trials was used. After a distraction task where the participants were shown a cooking video tutorial, the testing session started but without feedback (**Figure 1e**). Excepted a different order of presentation and the absence of feedback, the procedure was the same as well as the score of accuracy to reach to complete the task.

After the completion of the task, the participants were given the possibility to sleep. Before going to bed, they were instructed to put the Zmax headband, used to record brain activity and deliver auditory stimuli during REM sleep. The wire-up was remotely supervised in order to provide for guidance. Further instructions were also provided about how to turn off the device correctly, but also about data saving and sending.

During sleep, TMR was applied during REM sleep for all the participants using the laptop that they were instructed to put close to the bed. For that purpose, half of the short version of the sounds learnt during wake were pooled together and separated by a 2 sec. silence. This series was repeated as many times as possible. Due to intellectual properties, the lab did not get access to the algorithm used to detect and deliver cueing sounds. Hence, the criteria used to detect REM sleep and the number of repetitions were not controlled a priori. A manual inspection of the signal and the time of cueing sound permitted to confirm the absence of false positive cueing, namely, cueing sounds without justification. In the morning, the participants were instructed to stop the recording and send it to the examiners following a series of instructions given the day before. Any missing recording or issue with TMR cueing sounds during the night led to the exclusion of the participant. Due to 3 missing recordings and 1 technical issue about TMR, 4 participants were excluded from the final analysis of the present study.

The session 2 started around 10 am after 12 hours of sleep (**Figure 1e**). Although the instructions given were similar to the learning phase before sleep, the task comprised of premise and inference pairs. More precisely, participants were tested on their ability to recall the premise pairs learnt before sleep, but also on new item associations (**Figure 1d**) varying in distance degree, for a total of 10 premise and 20 inference pairs (e.g., AB; BA for the premise pairs or BD; DB for the inference pairs). The testing phase was repeated 3 times, always with a different pair ordering.

A week after the session 2, participants were asked to repeat the same sequence. For the session 3, the pairs were presented in a different order compared to session 2.

2.5 - Creation of time frequencies and EEG pre-processing

Datasets were extracted from participants EDF folders. Each folder contained a marker file with time duration of REM sleep and TMR. Periods of REM sleep and TMR were inspected visually. On that basis, the decision to select a 2 minutes duration of time series was based on the minimal amount of REM sleep and TMR application that all

the participants shared in common. EEG preprocessing was performed using EEGLAB (version 2022.0) toolbox from MATLAB. Due to the limited number of channels (F7 and F8) referenced to Fpz, no re-referencing was performed. The data were down sampled to 256Hz. A high-pass filter at 0.1 and a low-pass filter at 40 Hz was applied. The data was segmented into epochs of 2 seconds starting 500 Ms before stimulus onset and 1500 Ms after. Each trial was visually inspected and those that contained artifacts were manually removed. On that basis, two conditions were differentiated on a behavioural effect into "control" and "TMR". The condition "control" referred to the REM sleep portions that did not receive TMR stimulations while "TMR" condition referred to the portions of REM sleep for which the TMR cueing sounds were applied. Time-frequency analysis was performed using EEGLAB study while phase amplitude coupling (PAC) and epoch analysis were performed using Python. MNE package was used to import, visualize and analyze EEG, matplotlib.pyplot, SciPy and Tensorpac were used to plot the comodulograms, calculate the modulation index (MI) and perform the epochs t-test comparisons.

2.6 - Calculation of accuracy

Anchor pairs were excluded from the final calculation of the accuracy, and only probe pairs were considered for calculating accuracy. Anchor pairs, which consist of the first or last item in the hierarchy, were omitted because they tend to be easier to remember due to their consistent dominance or submissiveness.

2.7 - Selection of features of interest

The data analysis was preceded by a computational detection of features of interest. This process aimed to extract useful information from large data sets and avoid noisy features. The computational approach was a wrapper method, where a global model was calculated and trained based on the features from the dataset. Depending on their ability to explain the variance of the computed model, the features are saved or removed from the model by backward elimination. For that purpose, the method BORUTA was chosen (**see Prabhakaran, 2017 for detailed explanations about**

BORUTA application with Rstudio). BORUTA is a feature selection algorithm used in machine learning to identify the most important features for a given model. It operates by iteratively comparing the importance of real features with that of random features (shadows). This approach is based on the concept of random forest, which aims to capture the important features that can explain a particular outcome. The algorithm consists of two steps:

(**1**) The dataset is duplicated and a random forest classifier is trained to detect the important features by assigning a score for the mean decrease in impurity for each feature. A high score is associated with high importance. Three categories are formed. The "shadow min" includes the features with a low importance score, the "shadow mean" includes the features that are close to chance. Finally, the "shadow max" includes the features with high importance.

(**2**) The algorithm compares the importance of the duplicated features with that of the real dataset. After a certain number of iterations, a real feature is retained if it has a higher z-score than its shadow.

The importance score for each feature in the BORUTA analysis is derived from the importance measure provided by a random forest model. Random forest models, in turn, provide importance scores for each feature based on how much they improve the model's performance when they are included. A positive importance score indicates that the feature contributes positively to the predictive performance of the model. The higher the score, the more important the feature is deemed to be. A negative importance score implies that the feature detracts from the model's performance. This might seem counterintuitive, but it can occur for several reasons:

1/ The feature might be adding noise to the model, reducing its accuracy.

2/ The feature could be correlated with other features (multicollinearity), leading to unstable importance scores.

3/ The feature might interact poorly with other features (interaction effect) in a way that negatively impacts the model's overall performance.

2.8 - Model selection and calculation of parsimony

The parsimony and the quality of the models were assessed with the Mallow Cp (**see Bobbitt, 2021 for detailed explanations about Mallow Cp calculation with Rstudio**), a variant of AIC (Akaike Information Criteria) developed by Colin Mallows. Technically, the likelihood of a given model can be increased by adding more parameters. Thus, the more parameters used, the more informative the model. However, because the coefficient used (R^2) is a square, it cannot decrease as more parameters are added, which can improve the explanatory power of a model due to chance rather than the efficiency of its parameters. To limit this bias, the Mallow Cp was applied to assess the fit of the regression models on the basis of the features detected by BORUTA. The main objective here was to detect the most precise and accurate model that would need the lowest number of predictors to reach that precision. Among multiple models available, the one that exhibits the lowest Cp value is the most precise. Mallow Cp is calculated as follows:

Mallow Cp = (SSE_p / MSE_F) - (N - 2P)

. SSE_p = Sum of square errors for the potential model

. MSE_F= Mean square error of the full model

. P = number of predictors. The penalty N-2P represents the cost for a model that incorporate high number of predictors.

This method is consistent with the concept of parsimony, which aims to find a trade-off between the explanatory power of a model and its ease of use.

2.9 - Selection of unbiased effect sizes

The magnitude of the difference between means was described by using the Hedge's g. This effect size is the non-biased equivalent of the Cohen's d but for small sample size (n < 50). The formula used to calculate Hedge's g was:

Hedge g = (M1 - M2/ SD pooled) * (N - 3 / N - 2.25) * ((√N - 2) / N)

. M1 - M2 represent the mean difference.

. SD pooled is the weighted standard deviation

Finally, the adjusted R^2 was used as a coefficient of determination (**see Bobbitt, 2020 for detailed explanations about adjusted R^2 calculation with Rstudio**). This coefficient is consistent with the use of the AIC, as it captures the degree of parsimony of the model used. Technically, a malus is added to the R^2 if a predictor improves the model by less than chance. This process aims to avoid a natural increase in the R^2 value when predictors are added to the model, since the coefficient cannot decrease (a square is always positive). However, the penalty is reduced if a predictor is found to increase model accuracy more than by chance. The adjusted version of the R^2 is always lower than its biased version. The formula is presented as follows:

Adjusted $R^2 = 1 - (1 - R^2) (N - 1) / N - p - 1$

. N = sample size
. p = number of predictors

2.10 - Use of robust regressors

Due to the variability of the data observed, the classic ordinary least squares (OLS) estimator used to compute linear regression was associated with a robust regression estimator, the Theil-sen estimator. Instead of relying on every single data point equally like OLS does, the Theil-Sen estimator calculates the slopes and intercepts from various subgroups formed by combinations of a few data points. For instance, while estimating an intercept, the number of points in each subgroup (denoted as 'p') should be at least as many as the number of features ongoing dealing with, plus one. Once these slopes and intercepts are calculated, the final values are determined as what's called the 'spatial median' of all these different slopes and intercepts.

2.11 - EEG analysis

After being decomposed into epochs of 2 seconds, the EEG datasets were analyzed to extract the average time-frequency of each condition. The results were statistically compared to detect frequency of interests (theta and gamma range) susceptible to emerge from the TMR condition. On that basis, a PAC analysis was performed to detect coupling between the theta phase (4-8 Hz) and the gamma amplitude (30-40 Hz). PAC

strength was quantified by extracting the modulation index (MI). MI is a robust and reliable marker of coupling that ranges from 0 to 1, where higher coefficients are associated with a stronger coupling.

2.11.1 - Time frequency

The event-related spectral perturbation (ERSP) was performed using EEGLAB toolbox from MATLAB. The oscillatory power was obtain using a continuous wavelet transformation (Complex Morlet Waveform, 3 0.8 cycles). Concretely, the wavelet used to measure the amount and phase of the data in each successive, overlapping time window started with a 3 cycles wavelet (Hanning-tapered window applied). Then, the number of cycles in the wavelets used for higher frequencies expanded to reach 20% (1 minus 0.8) of the number of cycles in the equivalent FFT window at its highest frequency. The cycle number was chosen to propose a trade-off between a high frequency resolution and time resolution, as higher cycles tend to respectively increase the frequency and decrease the time resolution. Range of frequency was set to 0.5 to 40 Hz, resulting in a range of frequency analyzed from 3Hz to 40 Hz. Significant differences were performed with a permutation-based t-test with multiple comparison correction, n = 1000 randomizations and a statistical threshold set to 0.05.

2.11.2 - Phase-amplitude coupling (PAC) analysis and modulation index (MI)

Phase-amplitude analysis (PAC) was performed with Tensorpac from Python in a three-steps process. The phase and amplitude range chosen were respectively 1-10 Hz and 1-40 Hz. First, the Tort PAC method (Tort et al., 2008; 2010) was chosen to compute PAC, as this approach is known to exhibit a robust tolerance to noise and sensitivity to modulation width (Kramer et al., 2008; Amiri et al., 2016). Secondly, a surrogate computation using swap amplitude time blocks was performed. Concretely, amplitude values were shuffled within time blocks across trials. Using this approach helped to preserve the trial structure of the datasets for further analysis (significant amplitude t-test permutation by epoch). Moreover, it also provided a conservative estimate of PAC. As a final step analysis, a correction was applied using the dynamic

definition method. This method aimed to define frequency pairs based on the data characteristics or statistical criteria, a flexible method that adapts the properties of the dataset and provides for a strong ability to capture unexpected or nuanced couplings.

3 - Results

3.1 - Detection of features of interest

The first step started with a detection of features susceptible to explain the variation of inference accuracy within the participants. Since the depression score was shown to exhibit a narrow range of values, this feature was excluded to the analysis to avoid potential overestimations of shadow min boundary. Otherwise, the chronic insomnia and clinical anxiety anamnestic features were included as well as the session (session 2 versus session 3), the condition (control versus TMR), the premise pairs accuracy by pairs (AB, BC, CD…), the number of stimulation and finally the Modulation index (**Figure 2**). Although the maximum number of iterations was set to 800, only 335 were needed to classify the features.

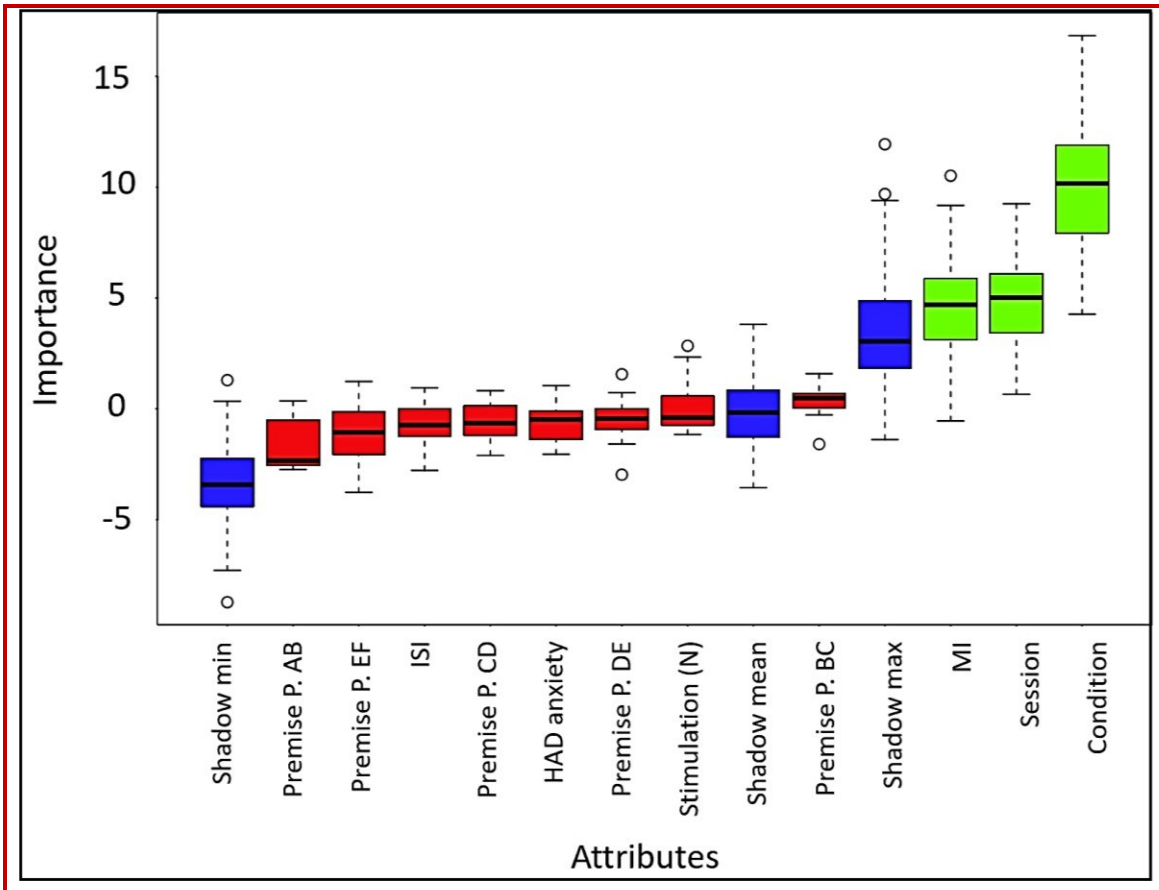


Figure 2: Classification of features of interest for inference pairs, sorted by degree of importance. The classification ended after 112 iterations. The three main features detected are the MI, the session time and the presence or not of TMR, each significantly higher than randomness effect represented by the shadows (blue boxplots).

BORUTA classification ended with the modulation index, the session and finally the condition features as best candidates to explain TI accuracy, with a significantly higher Mean Decrease Accuracy (MDA) than the shadows (representing randomness). On that basis, the following features were selected to create the combinations of models susceptible to explain the accuracy for the inference pairs:

. MI (The degree of associations between two brain waves, here theta and gamma)

. Session (Session 2 after sleep and session 3 for the follow-up)

. Condition (TMR versus no TMR)

3.2 - Comparison of model's parsimony

Based on the feature detection, a multi-model comparison was performed with the selected factors. The aim here was to assess the degree of parsimony of each model

to detect the one susceptible to propose the best trade-off between a high level of generalization and explanatory power (**Figure 3**).

The function ols_step_all_possible from the Rstudio package Olsrr was used to compute and test all possible models. Concretely, the following model inference pairs accuracy ~ TMR (YES vs NO) was chosen as the baseline model. During the process, all possible combinations were performed and compared by their predictors, namely the R^2, Adj. R^2 and Mallow's Cp. The multi-model comparison revealed 7 combinations. The baseline model analysis revealed a small explanatory coefficient (Adj. R^2 = 8.4%) associated with a decent Mallow's Cp (M. cp = 4.03). On that basis, the "session" feature was shown to improve the model (baseline + singularity), which exhibited a higher explanatory coefficient (Adj. R^2 = 9.1%) but associated with a higher Mallow's Cp (M. cp = 5.28.2) ($F(1, 109) = 0.75$, $p = 0.387$). Finally, the model 3 was created by adding the "MI", associated with a higher power of explanation (Adj. R^2 = 14.7%) and a more parsimonious accuracy (M. cp = 2.75) ($F(1, 109) = 3.28$, $p = 0.071$). On that basis, the model 3 was retained as the best model.

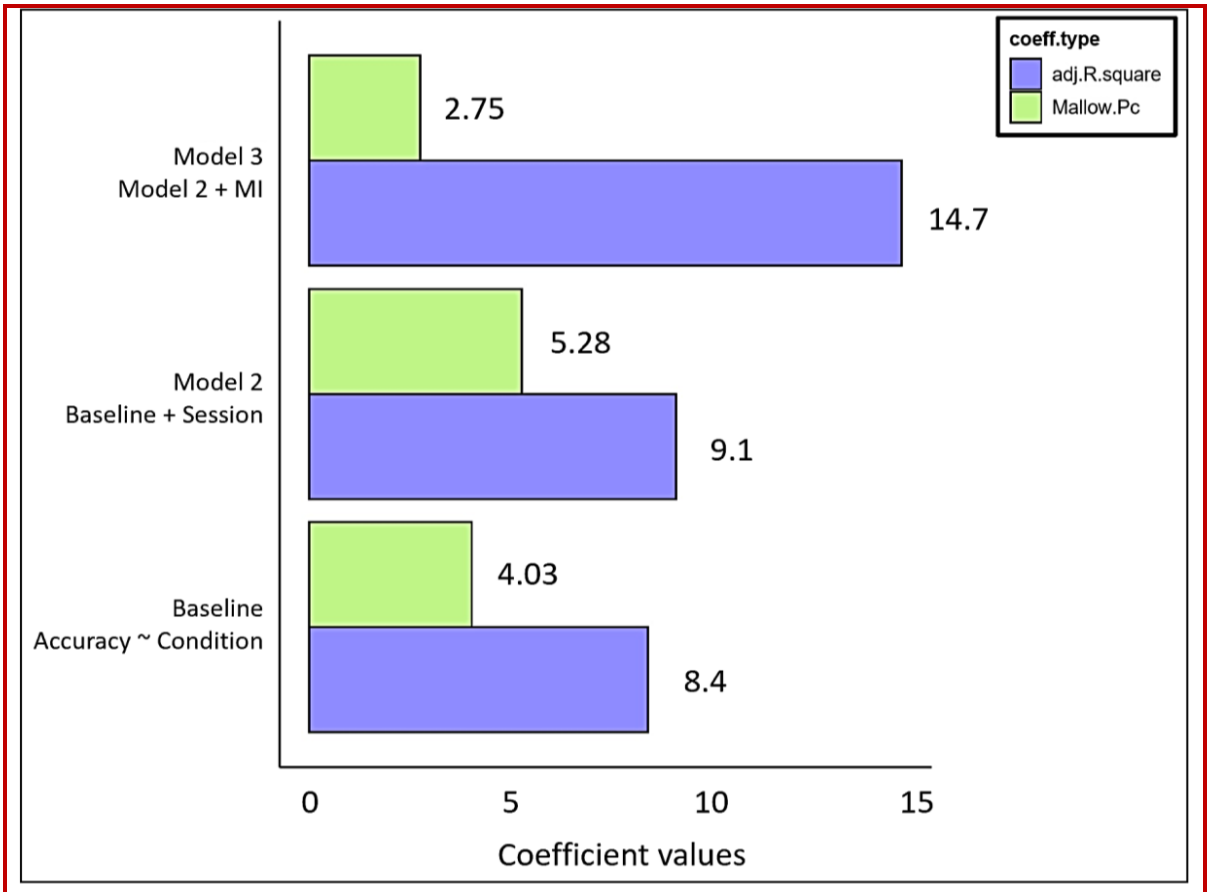


Figure 3: Graphical representation of model comparison between the baseline and the most parsimonious models for inference pairs. For each model, the adj. R^2 and Mallow's Cp were extracted and compared. An association between a small Mallow's Cp value and a high adj. R^2 coefficient is required to detect the most parsimonious and accurate model.

3.3 - TMR benefits on transitive inference are delayed in time

After sleep, comprising of TMR during REM or no stimulations, participants were tested on their delayed abilities to infer about new item associations 12 hours after learning and after a week (**see methods**). The absolute mean and the evolution rate between session 2 and 3 are presented **table 1**.

Firstly, a 2*2 ANOVA was performed to detect whether the session time (session 2 and session 3) by the TMR application (Yes versus No) could predict inference accuracy. The results revealed a condition ($F(1, 82) = 78.432$, $p = 1.68e\text{-}13$) and session-time ($F(1, 82) = 6.033$, $p = 0.0162$) but no interactions. Overall, the main findings revealed a positive but non-significant impact of TMR upon TI accuracy at session 2 (**Figure 4**), meaning 12 hours after sleep ($t(27) = 8.89$, $p = 0.157$, 95% CI

[-3.64, 21.43]; Hedge's g = 0.31, 95% CI [0.22, 0.83]). However, mean comparison at session 3 (**Figure 4**) revealed a strong and significant positive effect of TMR upon TI accuracy (t(27) = 26.17, p = 0.0008, 95% CI [11.91, 40.44]; Hedge's g = 0.97, 95% CI [0.41, 1.53]). Interestingly, comparison of the evolution rate between session 2 and 3 for both groups revealed a slight decrease but without any significant changing dynamics between sessions (-8.1%) for the NTMR group after a week. However, a delayed massive boost of performance was observed for the TMR group (+22.4%). If it is reasonable to suggest that applying TMR during REM may be associated with a delayed cognitive flexibility that would be the results of potential phenomenon of neural reorganization, it is also reasonable to notice that the positive evolutive trend observed could be the results of extreme values due to the small amount of inference pairs presented (6 pairs presented 3 times). The narrow range of response variability is highlighted by the sparse distribution curve.

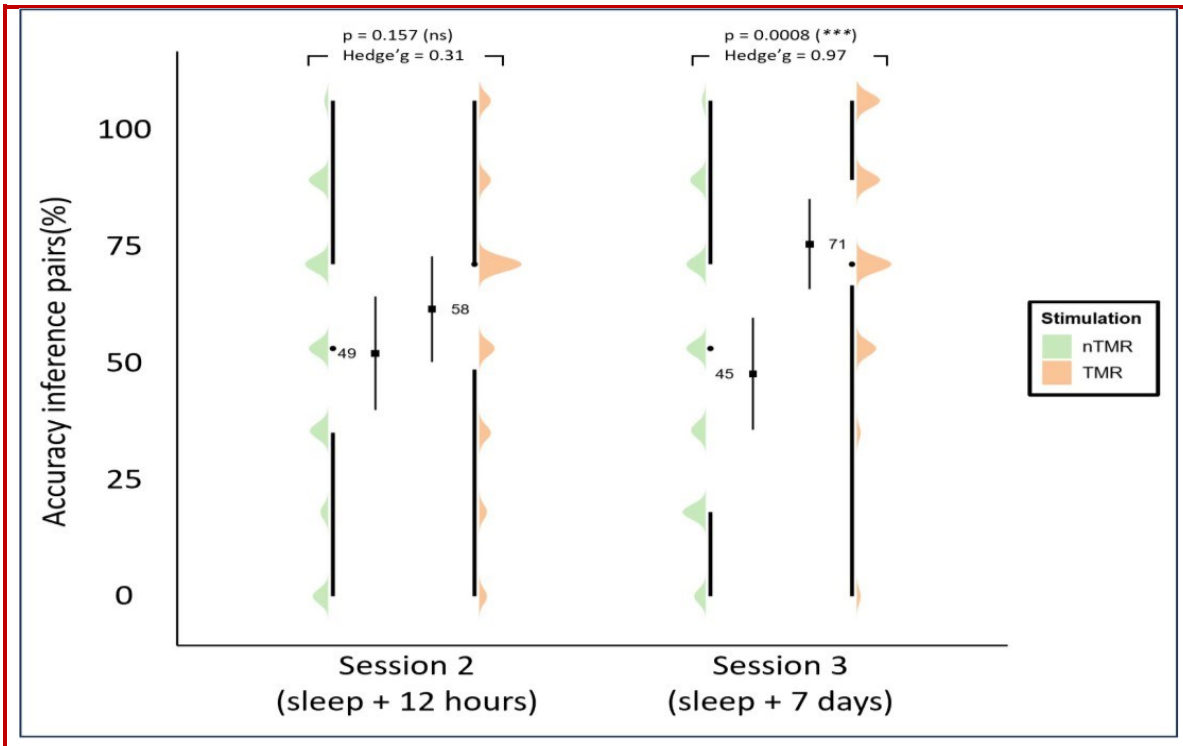


Figure 4: Accuracy for the inference pairs after 12 hours and after 7 days (N = 28 participants per groups). Dots and thick back lines are minimalist boxplot representations. Black squares and numbers are means and error bars are CI. ns = non-significant.

3.4 - EEG time-frequency comparison

To investigate word-elicited EEG activity, a time-frequency analyses on EEG epochs, then averaged across conditions and participants was performed. Via a cluster-based, two-tailed one-sample permutation test (1,000 randomization and a statistical threshold of 0.05) against zero across time points and frequency bands, three significant cluster, including an earlier delta-theta-alpha cluster (1–12 Hz) and a later alpha-sigma-beta cluster (9–25 Hz) were identified. For EEG responses (control versus TMR), the delta-theta cluster from -500 Ms to -300 Ms, the theta cluster from -500 to 0 Ms preceding stimulus onset, and finally the gamma cluster from 500 Ms to 800 Ms following stimulus (**Figure 5c**) were examined.

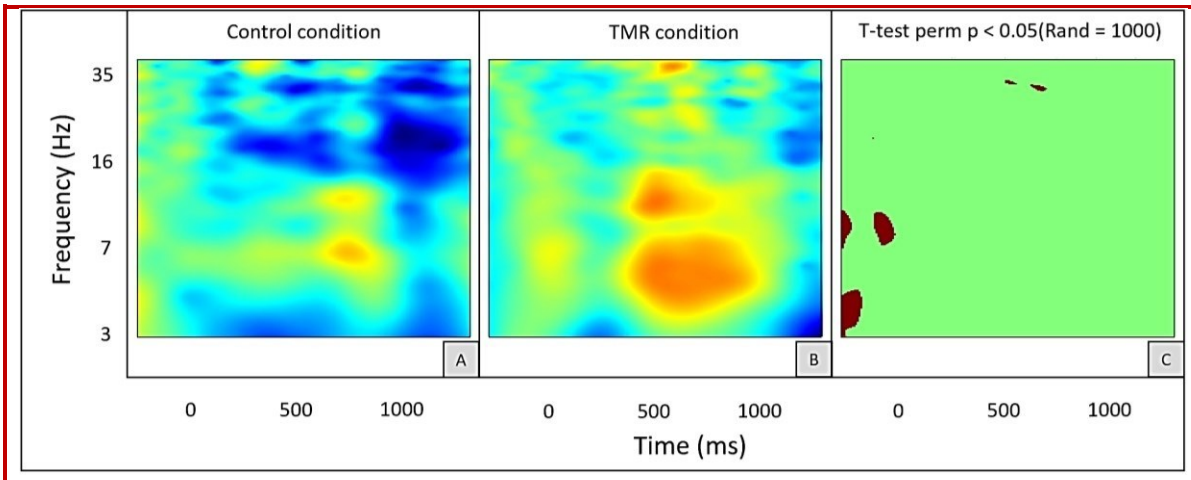


Figure 5: EEG differences between control TMR conditions. (**a**) Time-frequency ERSP control map across all participants. An increase of power can be observed around 700 ms following stimulus onset in the theta and sigma range. (**b**) Time-frequency ERSP TMR map across all participants. As well as control condition, the same cluster can be observed but at a much higher power. Additionally, a cluster in the low gamma range (35 Hz) appeared. (**c**) Permutation t-test map between condition. Although the main visual changes appeared after stimulus onset, the clusters of significant differences were detected around 500 Ms before stimulus onset, excepted for the gamma frequency.

Via a cluster-based, two-tailed one-sample permutation test (1,000 randomization and a statistical threshold of 0.05) against zero across time points and frequency bands, three significant cluster, including an earlier delta-theta-alpha cluster (1–12 Hz) and a later alpha-sigma-beta cluster (9–25 Hz) were identified. For EEG responses (control versus TMR), the delta-theta cluster from -500 Ms to -300 Ms, the theta cluster from -500 to 0 Ms preceding stimulus onset, and finally the gamma cluster from 500 Ms to 800 Ms following stimulus (**Figure 5c**) were examined.

These identified clusters were analyzed in the following analysis using Event-related desynchronization/synchronization (ERDS) components, relative power decreases or increases of electroencephalogram (EEG) in a specific frequency band (**Figure 6**). A paired sample t-test revealed a significant difference for the delta-theta cluster (t(77) = 2.06, p = 0.042, 95% CI [-0.01, 0.67]; Hedge's g = 0.02, 95% CI [-0.31, 0.31]), the theta cluster (t(77) = 2.24, p = 0.021, 95% CI [-0.03, 0.67]; Hedge's g = 0.01, 95% CI [-0.32, 0.3]), and the gamma cluster (t(77) = 2., p = 0.029, 95% CI [0.01, 0.58]; Hedge's g = 0.01, 95% CI [-0.31, 0.34]) (**Figure 6**).

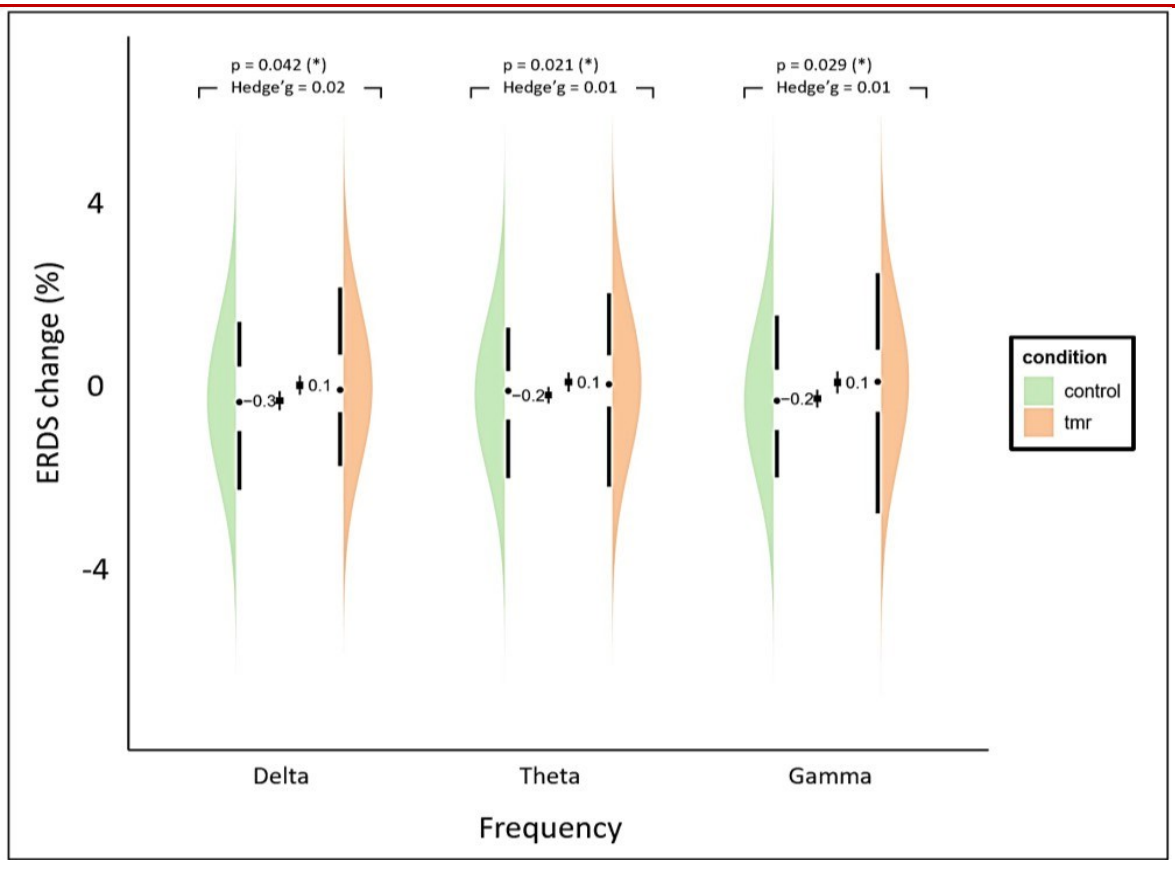


Figure 6: ERDS percentage of power changes for the delta, theta and gamma clusters (N = 28 participants per groups). Dots and thick back lines are minimalist boxplot representations. Black squares and numbers are means and error bars are CI. ns = non-significant.

Taken together, these findings suggest a benefit from TMR application in the power increase of delta, theta and gamma range. These results are in line with the rhythmic slow activity often coupled with gamma frequency and that can be observed in both humans (Bodizs and al., 2001; Clemens and al., 2009) and rodents (Bland and Whishaw, 1976). Although RSA implication is unclear, multiple findings suggest a

crucial role in memory integration (Bódizs and al., 2001; Nuñez and Buño, 2021). A summary of the results is presented **Table 1**.

3.5 - Theta-gamma PAC modulated by TMR

The next step of the analysis aimed to examine changes in phase-amplitude coupling (PAC) between theta and low-gamma frequency (**Figure 7**), by comparing the modulation index (MI) between conditions (**Figure 8**). For that purpose, the theta phase (4-8 Hz) on low-gamma (30-40 Hz) was extracted from participant's sleeping brain activity after learning premises.

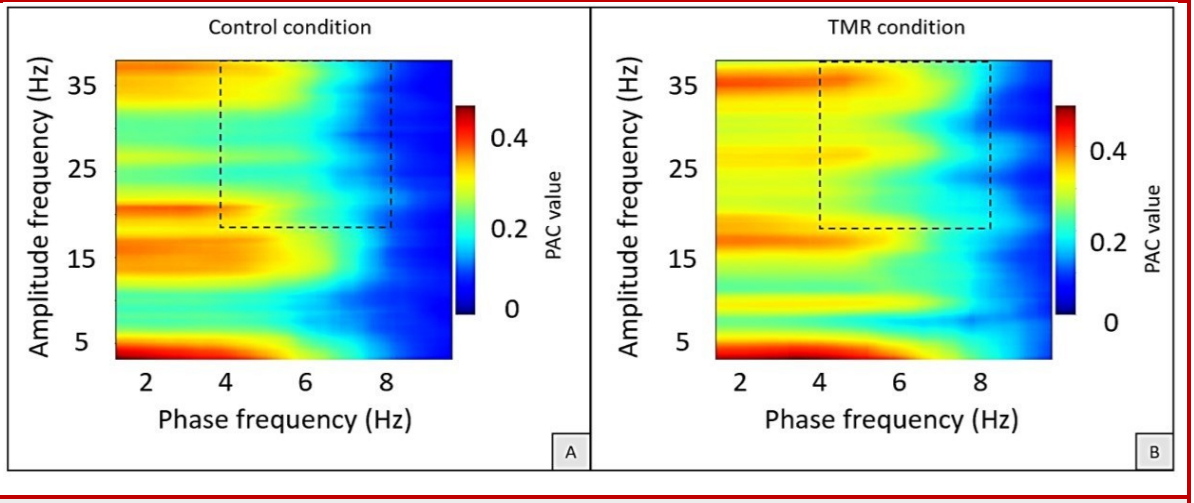


Figure 7: PAC representation averaged between participants. (**a**) Cross frequency spectrogram for the control group reveals a delta (2-4 Hz) and low theta (4-6 Hz) phase-locked with a large sigma (13-15 Hz), beta (15-20 Hz) and low gamma range (32-40 Hz). (**b**) After TMR application, coupling dynamics tends to decrease for the delta and sigma frequencies but to increase in the low theta and gamma range. Modulation index between phase and amplitude is averaged by participants. Black square represented by the dotted lines represents the region of interest.

Due to the aim of the study, the potential coupling between delta and spindle activity, though interesting due to its supposed role in memory formation during SWS has not been considered for further analysis. Instead, the PAC analysis aimed to focus to the coupling between theta and gamma activity. PAC value has been extracted for all the participants in the range of 4-6 Hz for the theta phase and 30-35 Hz for the gamma amplitude and then averaged by conditions. PAC values were computed in a three-step process (see methods) using Python Tensorpac package that comprised the Tort PAC approach, a swap amplitude time block surrogate computation and finally a

dynamic definition correction. Though a small MI value (**Figure 8**), the paired t-test analysis performed between conditions revealed a strong significant difference (t(27) = 5.18, p = 1.87e-05, 95% CI [0.3, 8.57]; Hedge's g = 1.49, 95% CI [0.89, 2.09]). A summary of the results is presented **Table 1**. Next and final part of PAC analysis aimed to investigate about how applying TMR could modulate gamma phase distribution over theta band. For that purpose, a permutation t-test was performed at $p < 0.05$ threshold with n = 1000 randomizations. Again, the time period for which TMR was applied exhibited a stronger coupling between theta and gamma range (**Figure 9b**) compared to the control condition (**Figure 9a**).

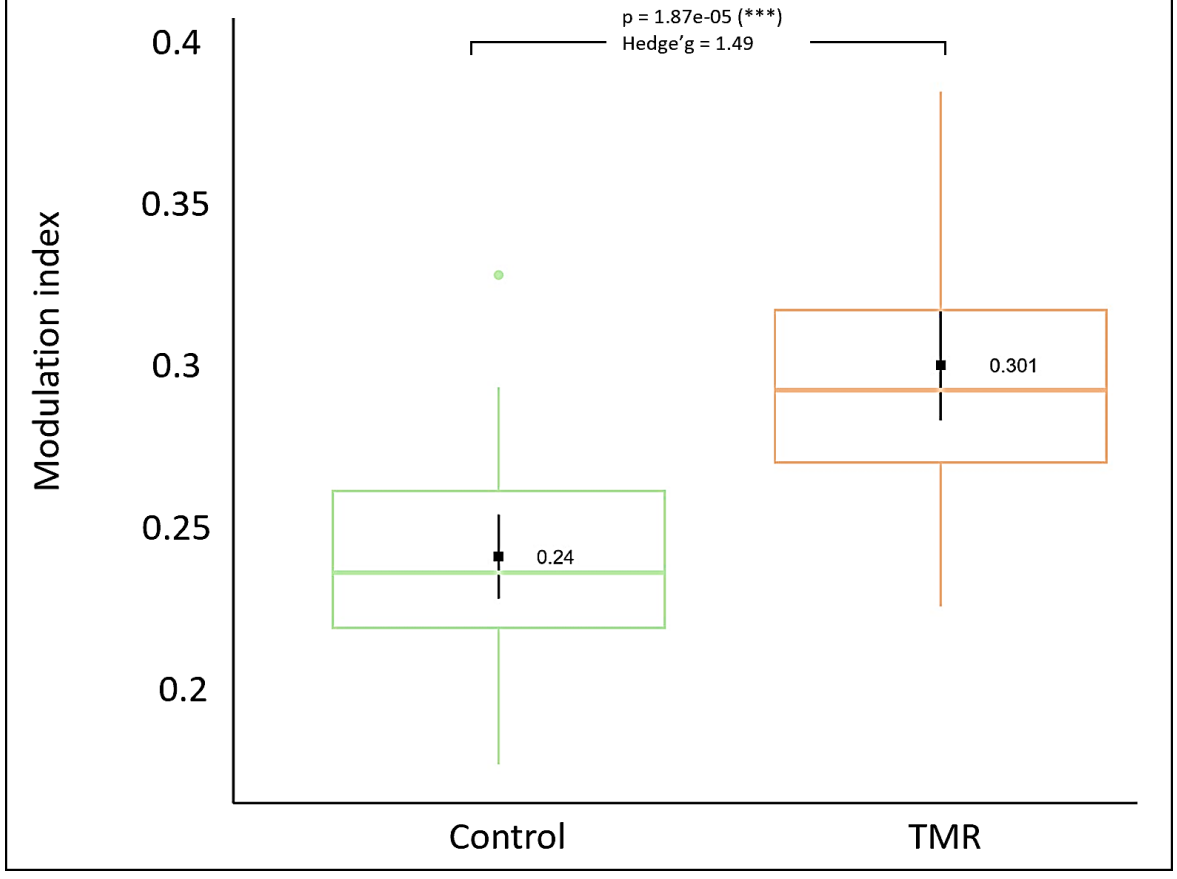


Figure 8: MI representation averaged between participants. Phase theta (4-6 Hz) and low gamma amplitude (30-35 Hz) is significantly modulated by TMR application during REM sleep. Black squares and numbers are means and error bars are CI. ns = non-significant.

However, and surprisingly, gamma frequencies from TMR condition appeared to be preferentially and significantly phase-locked to the down-state of the theta phase (from 90° to 225°) whereas gamma from the control condition revealed a significant

phase-locking to the up-state (from 270° to 45°) of theta frequency (**Figure 9c**). Finally, a PAC time analysis using a permutation t-test was perform to detect any dynamic strengths of coupling between epochs (**Figure 9c**). Firstly, the amplitude frequency range confirmed the theta phase coupling with low gamma amplitude (28 to 36 Hz). Secondly, and despite a small number of significant epochs between condition, the significance appeared to be uniformly distributed over epochs. However, and interestingly, the gamma range was shown to progressively decrease over epochs.

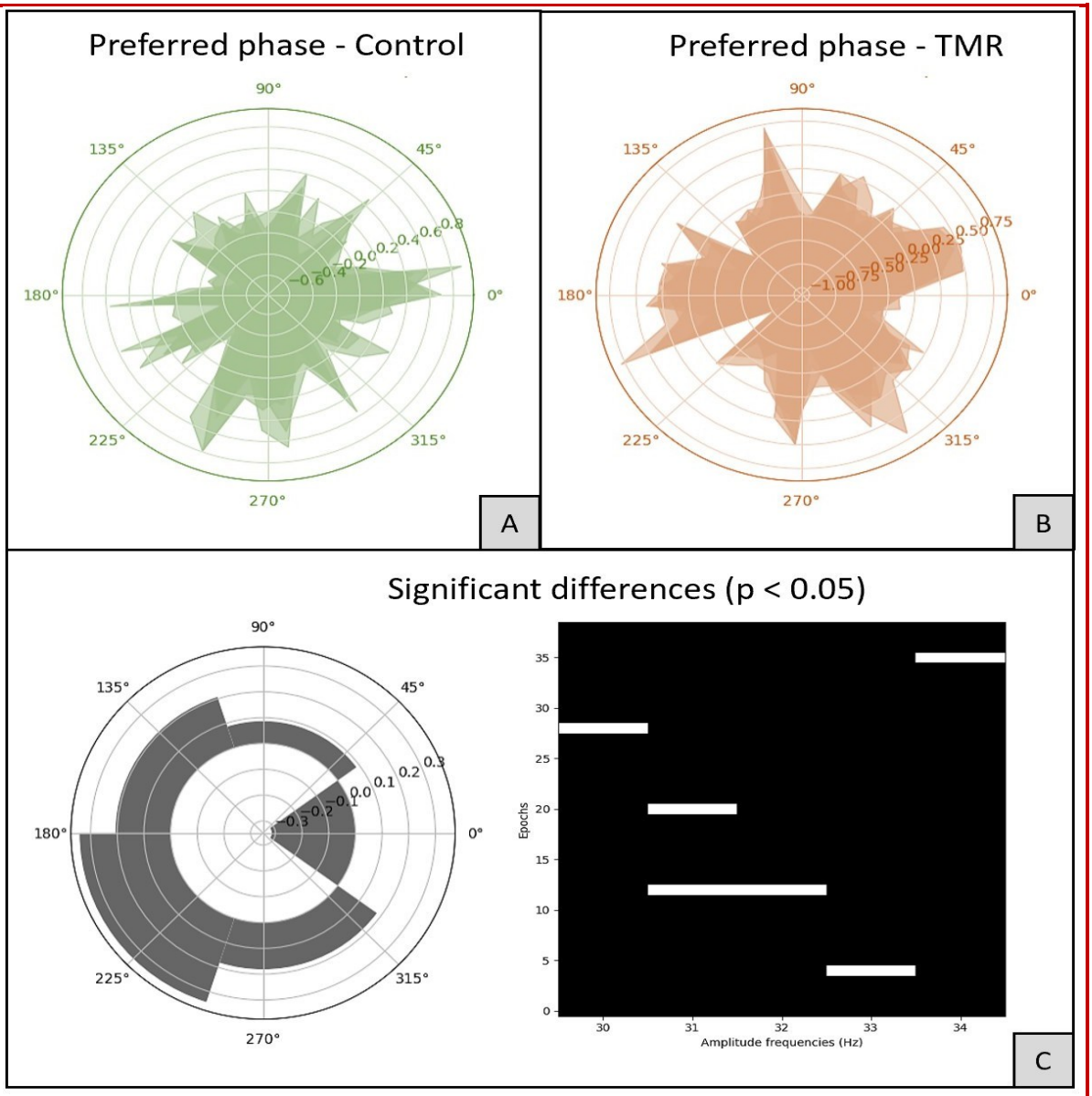


Figure 9: Phase-preference between theta and low gamma amplitude. (**a**) Phase- preference between theta phase and gamma amplitude for the control condition. (**b**) Phase-preference between theta phase and gamma amplitude for the TMR group. (**c**) Representation of significant difference of phase-preference between conditions (left) and temporal comparison between epochs (right).

However, and interestingly, the gamma range was shown to progressively decrease over epochs. This observation is in line with the different but complementary assumptions whereby a reduction of gamma oscillation would be the reflect of neural habituation (Moldakarimov et al., 2010) or an increase of successful progressive memory integration (Madhavan et al., 2015). This interpretation is also in line with the time-frequency analysis that revealed a significant gamma cluster around 650 Ms after TMR cueing sound. Hence, it is reasonable to assume that progressive decrease in gamma band would be the illustration of a progressive integration of premise pairs over epochs.

3.6 - Theta-gamma PAC and TMR benefits in transitive inference

So far, TMR application during REM sleep has been shown to promote coupling between theta and gamma frequencies and increase the strength of it. Moreover, at the behavioural level, TMR appeared to promote transitive inference abilities, leading to a higher performance compared to control condition, especially after a week. Building on these findings, the last part of the present analysis aimed to assess whether the strength of coupling represented by the modulation index could predict TI accuracy at short and long term. Because of a high degree of variability, the classic linear approach based on the ordinary least squares (OLS) estimator has been associated with the Theil-Sen estimator, much robust against outliers (see methods). Its standout feature is its ability to handle roughly up to 29.3% of corrupted or outlier data points in a simple linear regression scenario. More specifically, Theil-sen estimator finds the 'middle ground' among many slopes and intercepts calculated from different smaller groups of data points, rather than solely relying on all data points equally like OLS.

The preliminary results based on the model accuracy ~ MI + condition + session revealed a global significant relationship ($F(3, 108) = 4.99$, $adj.R^2 = 0.097$, $p = 0.002$). However, none of the features, taken separately, manage to predict the accuracy (condition P.value = 0.104; session P.value = 0.388) excepted the MI ($p = 0.0735$) close to significance. Since Theil-sen regression only fits with bivariate models, the

global model was split by condition and session, resulting in four different models (**Figure 10**).

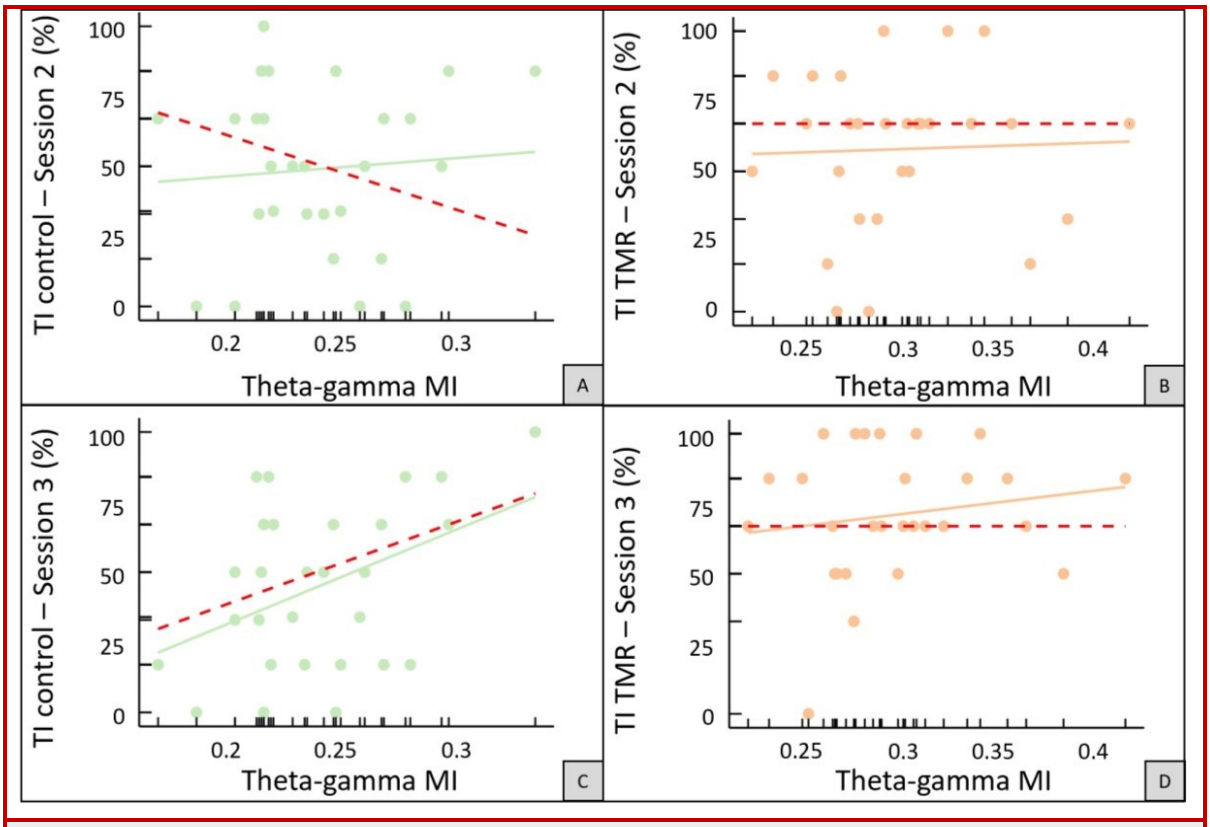


Figure 10: Representation of the relationship between the MI, representing the strength of coupling between theta and gamma frequency, and the transitive inference accuracy per sessions and conditions. Plain and red dashed lines respectively represent the linear (OLS) and Theil-sen estimators. (**a**) Relationship after sleep for the control group. Due to its robustness, the Theil-sen regression revealed the negative and surprising relationship between MI and TI accuracy. (**b**) Relationship after sleep for the TMR. The flat trends revealed by OLS and Theil-sen approach is in line with the huge variability of the data. (**c**) Relationship at follow-up for the control group. (**d**) Relationship at follow-up for the TMR group.

Theil-sen regression clearly revealed its robustness against outliers when assessing the relationship between MI and accuracy after sleep for the control condition. Indeed, although the classic linear fitting line revealed a positive trend, the Theil-sen one (red dashed line) revealed a negative relationship (**Figure 10a**). On that basis, no significant relationship was found ($F(1, 26) = 0.168$, adj.$R^2 = 0$, Pseudo $R^2 = 0$, $p = 0.685$, Theil-sen $p = 0.115$). In line with the control group, the TMR condition did not reveal a significant relationship between MI and TI accuracy (**Figure 10b**) ($F(1, 26) = 0.036$, adj.$R^2 = 0$, Pseudo $R^2 = 0$, $p = 0.851$, Theil-sen $p = 0.118$). Interestingly, a significant relationship was found at follow-up for the control group (**Figure 10c**),

assuming a positive delayed effect of sleep ($F(1, 26) = 5.569$, adj.$R^2 = 0.14$, Pseudo $R^2 = 0.13$, $p = 0.026$, Theil-sen $p = 0.023$). Though a lower relationship found by the Theil-sen estimator compared to the OLS one, their observation reached the same conclusion, suggesting a strong trustfulness of the results. Finally, and surprisingly, the positive relationship found in the control group did not appear in the TMR group ($F(1, 26) = 0.689$, adj.$R^2 = 0$, Pseudo $R^2 = 0.01$, $p = 0.413$, Theil-sen $p = 0.059$) as shown by the flat trend revealed by the Theil-sen estimation (**Figure 10d**), though a p-value close to significance. A summary of the results is presented Table 2.

4 - Summary of the main findings

The present section aims to present a brief summary of the behavioural and electrophysiological findings from this study (**see Table 1**). Negative findings, non-significant p-values or marginal effect size are represented in red. TS.p represents the p-value calculated on the basis of Theil-sen estimator. Ps.R is the pseudo R^2 calculated with the Theil-sen approach.

Table 1 | Summary of the behavioural and EEG findings

	Statistical results	
Test procedure	P-value	Effect size
Behavioural findings		
ctrl vs. TMR S2	p = 0.157	Hedge's g = 0.31
ctrl vs. TMR S3	p = 0.0008	Hedge's g = 0.97
ER ctrl S2.S3	-	-8.1%
ER TMR S2.S3	-	+22.4%
Electrophysiological findings (Modulation index)		
ctrl vs. TMR delta	p = 0.042	Hedge's g = 0.02
ctrl vs. TMR theta	p = 0.021	Hedge's g = 0.01
ctrl vs. TMR gamma	p = 0.029	Hedge's g = 0.01
MI ctrl vs. TMR	p = 1.87e^{-05}	Hedge's g = 1.49
Electrophysiological correlates of transitive inference accuracy		
Accuracy ~ MI (ctrl S2)	p = 0.685, TS.p = 0.115	adj.R^2 = 0, Ps.R^2 = 0
Accuracy ~ MI (TMR S2)	p = 0.851, TS.p = 0.118	adj.R^2 = 0, Ps.R^2 = 0
Accuracy ~ MI (ctrl S3)	p = 0.026, TS.p = 0.023	adj.R^2 = 0.14, Ps.R^2 = 0.1
Accuracy ~ MI (TMR S3)	p = 0.413, TS.p = 0.059	adj.R^2 = 0, Ps.R^2 = 0.01

5 - Discussion

Sleep, an indispensable physiological process, has long been recognized for its significant role in memory consolidation and various cognitive functions, including executive functions and mood regulation. However, the precise mechanisms underlying protective sleep effect against long-term memory decay and its impact on transitive inference, a specific form of relational memory involving the deduction of novel relationships from existing knowledge associations, remain unclear. Thus, the aim of this study was to contribute to the existing body of knowledge by investigating the potential modulatory effect of sleep on transitive inference and memory consolidation over both short and long-term intervals. For that purpose, targeted-memory reactivation (TMR) was applied during Rapid Eye Movement (REM) sleep, a sleep stage thought to play a pivotal role in memory reorganization according to the BiOTA model. A secondary objective was to identify neural correlates that might explain the potential cognitive benefits of sleep. While numerous studies have provided valuable insights through methods such as Event-Related Potentials (ERPs), time-frequency analysis, and EEG representational similarity analysis (RSA), the present study aimed to investigate about cross-frequency coupling between theta and gamma activity in humans, a coupling known to play a crucial role in memory integration (Canolty et al., 2006; Axmacher et al., 2010; Koster, 2018). To do so, this study evaluated participants' inference accuracy after a full night of sleep and after one week to gain insights into the evolution of sleep-related benefits on accuracy over short and long-term intervals. On that basis, the strength of coupling, represented by the theta/gamma modulation index was extracted and used as the primary predictor of accuracy variability between participants and across different sleep conditions. MI was then tested as a potential correlate of TI accuracy at short and long-term using OLS and Theil-sen estimator.

Firstly, behavioural findings from TMR condition revealed an interesting increase of transitive inference accuracy compared to immediate testing after sleep, a week after learning. Such a delayed effect did not appear in the control condition. Importantly,

sleep-related benefits did not appear to promote TI higher than chance, irrespective of the testing session. These findings go against the sleep benefits upon TI (Bowden et al., 2005; Luo et Knoblich, 2007; Kumaran, 2013) and the memory integration promoting effects of theta/gamma coupling (Canolty et al., 2006; Axmacher et al., 2010; Koster, 2018) raised in the literature. Hence, it becomes reasonable to suggest that the mixed combination between cued and uncued items might have impaired to spontaneous associations between premise pairs, leading to a loss of sleep benefits.

On the other hand, the increase of theta/gamma coupling in the TMR condition might explain the behavioural benefits observed after sleep and at greater extent after a week. Although the exact reasons of such a difference between TMR and sleep are unclear, it is possible to posit that TMR provided a support of relational memory process, thus providing a "compensation" against the impairment of sleep benefits. Taken together, these findings are in line with the iOtA and BiOtA models presented by Lewis et al., (Lewis and Durrant, 2011; Lewis et al., 2018) in which overlapping memory representations are stored for a future integration. Here, the mixed combination between cued and uncued premise pairs might have affected overlapping between premise representations, resulting in weaker boundaries between these representations. The second model, in line with the promoting effects of theta/gamma coupling (Canolty et al., 2006; Axmacher et al., 2010; Koster, 2018) in memory integration, posits that REM sleep would promote integration of overlapping representations. Here, it can be proposed that due to the weak associations between representation, spontaneous theta/gamma coupling observed in the control condition (without TMR) might not have been high enough to induce memory integration, contrarily to TMR-related benefits upon the theta/gamma coupling that compensated the altered boundaries between representations, leading to their integration. Although these conclusions might appear speculative, they provide founded and insightful information about the process of integration of memory overlapping during sleep and the mechanisms involved. However, the reason why significant TMR benefits only appeared after a week are unclear, excepted potential illustration of "slow form of plasticity" as raised by Pereira et al., (Pereira et al., 2023). At the EEG level and as expected, time-frequency analysis, revealed significant theta gamma clusters

respectively 200 Ms before and 500 Ms after stimulus onset. Here again, the lack of physiological analysis makes the interpretation quite challenging. However, a potential progressive integration of hierarchy between items, promoted by TMR, leading to a subsequent gamma activity is in line with the theta gamma coupling interaction discussed in the literature (Bosman et al., 2012; Clouter et al., 2017; Köster et al., 2017). Moreover, a deeper EEG analysis of cross frequency between theta and gamma activity revealed a significant effect of TMR on the strength of coupling for the theta and low gamma range (around 35 Hz). Specifically, the modulation index, a marker of coupling strength, increased with TMR application. Surprisingly, the amplitude of gamma signal appeared to progressively decrease, as a potential sign of neural habituation (Moldakarimov et al., 2010) or integration of memory (Madhavan et al., 2015). Surprisingly, EEG coupling did not appear to vary in terms of strength but also in terms of characteristics and typology as gamma amplitude appeared to be phase-locked to the up-phase of theta band for the control condition, and phase-locked to the up-phase of theta for the TMR condition. At this stage, no convincing explanations can be provided to explain the reasons about this difference, and the consequences. As recent studies have raised the importance of phase-locking during slow-wave sleep studies in subsequent memory performance (Ngo and Staresina, 2022; Santamaria et al., 2023), it is reasonable to suggest that theta gamma coupling during upon down-state could differ in their ability to promote memory integration. Further studies are needed to clarify this point. Finally, and at first sight, MI values did not appear as convincing neural correlates of transitive inference abilities. However, building on the findings from behavioural results and the findings about the difference in phase-locking, a plausible scenario can be proposed. Indeed, assuming that the delayed behavioural effect observed between conditions is the illustration of a slow plasticity phenomenon, the lack of relationship between MI and immediate testing after sleep is not surprising. In a second time, whether only control condition revealed a delayed relationship between MI and accuracy could be explained by the fact that down-state coupling in the TMR condition may have impaired memory integration, as TMR during down-state of slow oscillation were reported to do.

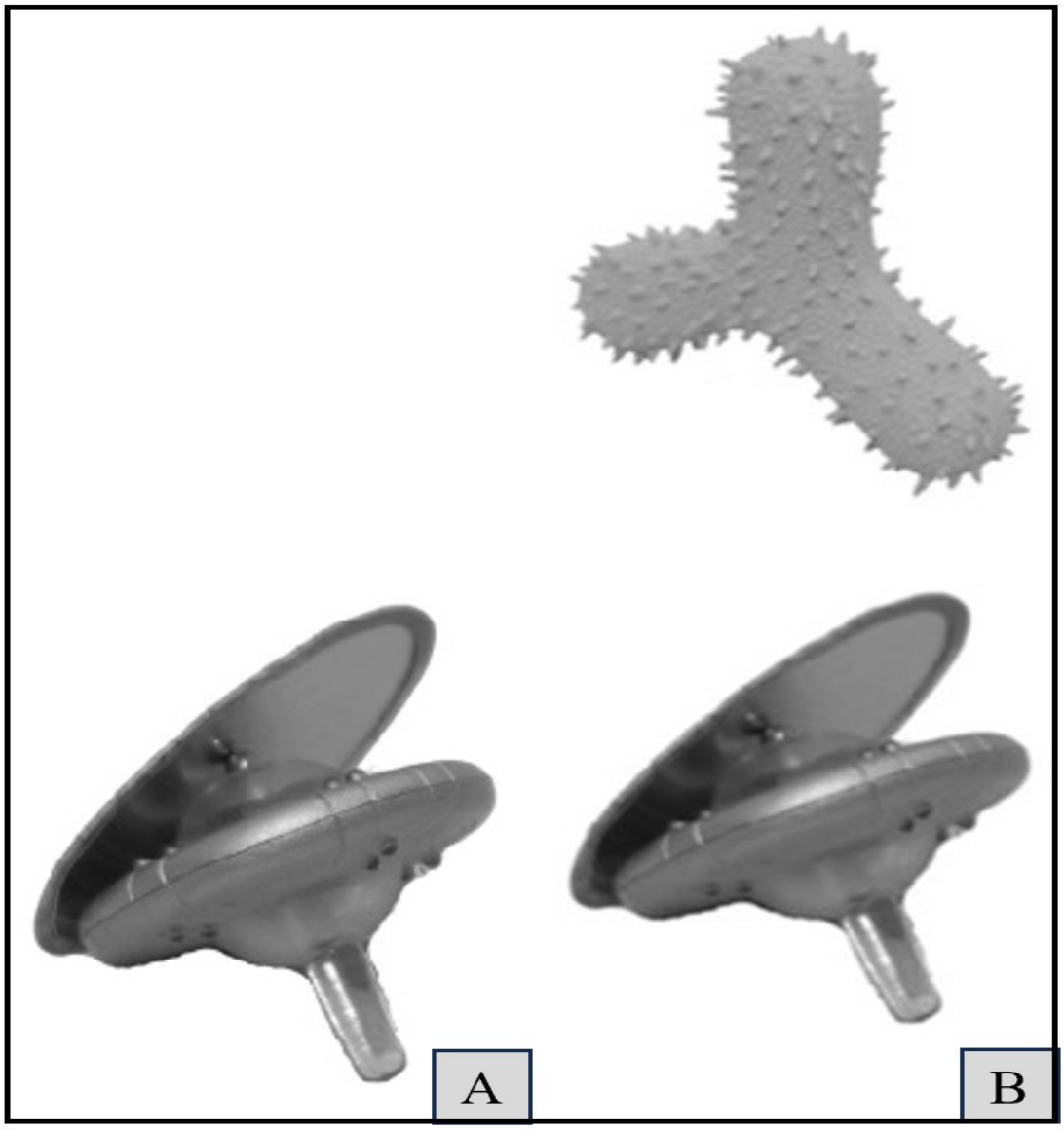
Although the present study led to insightful findings about TMR and REM sleep

implication in cognitive flexibility through theta/gamma coupling, especially in humans, it is essential to acknowledge several limitations of this study. First, data collection occurred during the early stages of the COVID-19 pandemic, characterized by stress and potential depressive factors related to public health measures and the overall context. This context's impact on mood, sleep quality, and cognitive functions should be considered when generalizing the findings to different circumstances. Second, the study was conducted remotely due to the pandemic, and while participants were provided with guidance to create a quiet environment, replicating laboratory conditions at home presented challenges, possibly affecting accuracy due to sources of disturbance. Another source of limitation may arise from the combined hierarchies. Indeed, in order to simplify the task, only one set of items was proposed to the participants, comprising of items to be stimulated by TMR or not. This approach differs from the traditional transitive inference approach that consists in learning a set of items without TMR, and second one with TMR. Consequently, it cannot be excluded that the present approach may have impaired the process of rule integration. Resulting from the decision to combine TMR and non-TMR pairs within the same set of items, only a few pairs were considered as "pure" TMR (CE and EC repeated 3 times) and non-TMR (BD and DB repeated 3 times) pairs, namely pairs that comprised two items with TMR or without TMR. As a consequence, the continuity of the data became impaired and tended to be clustered, resulting in a lack of visibility of the potential effects of TMR. Finally, and due to the lack of controlled TMR stimulation provided by the remote content of the present study, a small number of epochs has been extracted by participants (40 per conditions), leading to a potential source of validity violation.

In summary, and despite of these limitations, cross-coupling EEG analysis of TMR benefits during REM sleep has yielded valuable insights into the role of sleep benefits in memory consolidation and cognitive adaptability. Significantly, a remote TMR application during REM sleep has, for the first time, demonstrated its capacity to capture variations in performance in the realm of sleep research and home-based TMR protocols. With its ability to capture the advantages of sleep using simple, home-based devices equipped with a limited number of channels, TMR protocols present a novel and promising perspective for TMR applications in real-life scenarios. Indeed, in a

world where approximately 62% of adults feel they do not get enough sleep, it is reasonable to imagine a future where a straightforward MI coefficient, easier to interpret than a complete EEG analysis, administered following a full night of sleep, could monitor and potentially enhance sleep habits, optimize the onset of sleep phases, and provide valuable support in managing mood disorders.

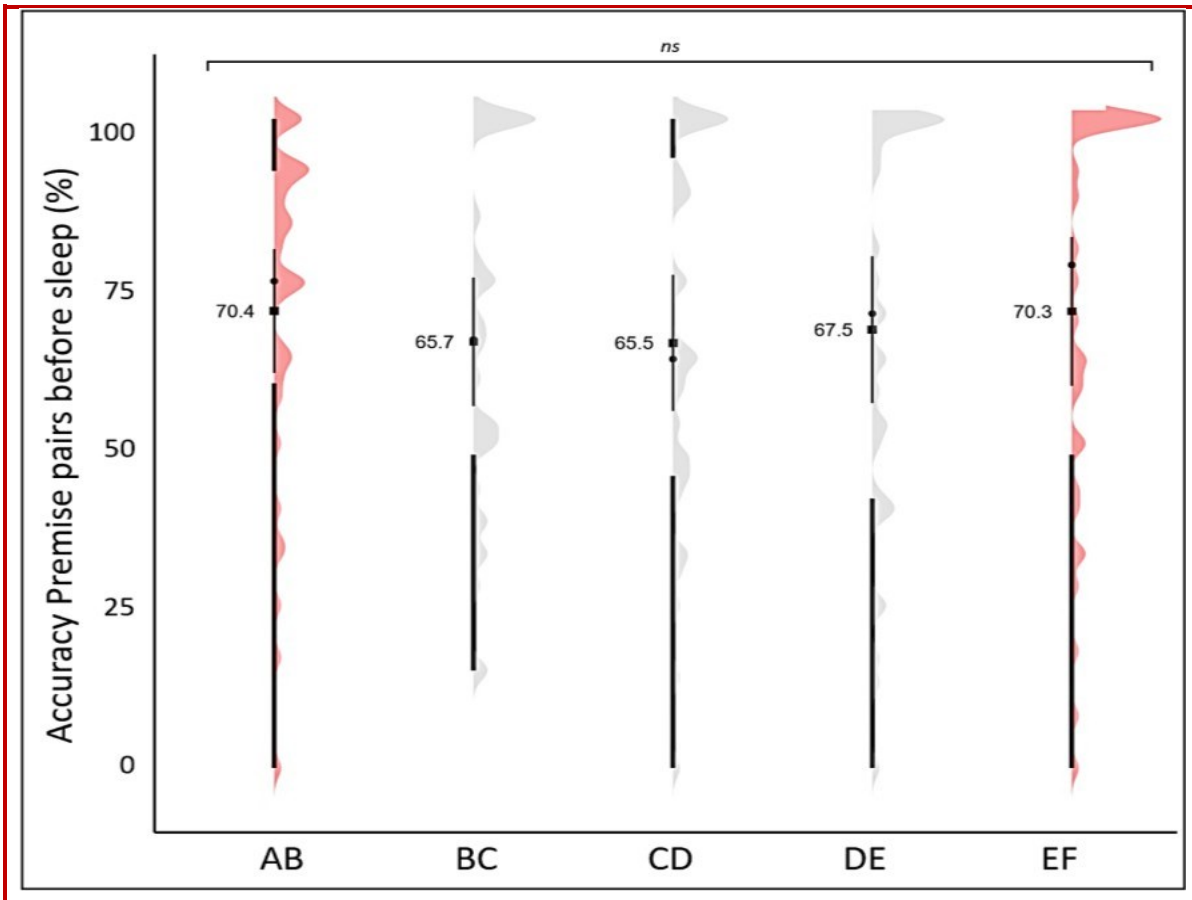
6 - Supplements



S1: Presentation of the items used for the purpose of this study. (**a**) This imaginary item was extracted from a database. The background has been removed and the contrast has been changed to avoid bias or disturbance for the participant. (**b**) Presentation of the top/down structure of one pair.

TABLE 2 | Polysomnographic characteristics

	Percentage of sleep stage
Stages	**Mean (SD) %**
Stage N1	6.49 (3.18)
Stage N2	57.9 (10.3)
Stage N3	16.6 (8.4)
REM sleep	18.9 (8)
SE	76.5 (13.5)



S2: Graphical representation of premise pairs accuracy before sleep. The red pairs (AB and EF) are called anchor pairs and show a higher accuracy as expected since within this series, these pairs benefit from the primacy and recency recall. Moreover, A is always dominant whereas F is always submissive. ns = non-significant.

Chapter 4: TMR APPLICATION IN SWS: DELTA/SPINDLE AND DELTA/GAMMA AS MARKERS OF TRANSITIVE INFERENCE?

Abstract

Although the crucial role of slow-wave sleep in the improvement of memory consolidation is globally admitted, the impact upon higher cognitive functions, namely transitive inference, as well as the potential benefits of targeted-memory reactivation, is still unclear. According to the iOTA model, SWS sleep would play a crucial role in the capacity to reorganize events to be consolidated and the idiosyncratic ones to be removed. While recent findings have highlighted the importance to consider the phase amplitude coupling between delta-gamma and delta-sigma, as well as the phase preference of delta oscillations, the present study aimed to investigate about neural correlates of cognitive flexibility. On that basis, participants were trained on two sets of hierarchically related pictures of imaginary objects. Following training, sleeping brain activity was recorded while one series has been reactivated with TMR during SWS while the other one served as control. Phase-amplitude coupling strength of delta-gamma and delta-spindle, represented by the modulation index was extracted as a potential predictor of performance. After being tested on their transitive inference ability at short (12 hours after learning) and long-term (7 days after learning), behavioural findings revealed a significant TMR-related benefits upon TI accuracy at short and long term. However, at the physiological level, neither the delta-gamma coupling, nor the delta-spindle one managed to predict accuracy. Taken together, these findings provide for encouraging results about sleep's role in cognitive flexibility and TMR boosting effect, provide no support for a role of delta-gamma coupling in this.

1 - Introduction

Being able to focus on multiple high-stakes tasks at once, coming up with a novel idea under the pressure of a deadline, taking a new route to avoid bad traffic, create a new recipe for dinner because ingredients are missing, cognitive flexibility allows to observe a situation and alter decisions to best fit both needs and the current situation at hand. Not only a key success in the workplace, cognitive flexibility is part of everyday life. Among the helpful cognitive mechanisms that can be used to solve issues, improve creativity or promote flexible thinking to adapt to various situations, transitive inference (TI) is a widely used holistic cognitive process defined by the ability to build new assumptions (AC) or strategies based on premises (AB and BC) and that is thought to emerge late in development in humans (Piaget, 1960; Bryant and Trabasso, 1971). As an example, transitive inference may come into play when dealing with the formation of professional or social circles. In the case of a business partnership, it can be crucial to guess on basis that a company A has a partnership with the company B that itself is competing with the company C, that companies A and C may also compete with each other.

While the shape of cognitive flexibility can take multiple expressions such as reasoning, inhibition, mental flexibility, or planification, a full comprehension of cognitive flexibility mechanisms may appear challenging. However, decades of research have brought convincing findings whereby the insight resulting from the associations between distant premises in TI would be fostered by sleep (Bowden et al., 2005; Luo and Knoblich, 2007; Kumaran, 2013). Recent cognitive models, namely the iOtA and BiOtA models, suggest that sleep would promote the formation of new connections between past and recent events that shares semantic representations (Lewis and Durrant, 2011; Lewis et al., 2018), in order to improve issue-solving skills (Sanders et al., 2019), rule comprehension (Batterink et al., 2014) and above all, inferential reasoning (Ellenbogen et al., 2007; Werchan and Gómez, 2013; Behrens et al., 2018; Aly et al., 2022). However, and importantly, findings from sleep-related benefits upon relational memory have been challenged by numerous contradictory findings. For instance, a

study comparing the effects of sleep versus incubation on riddles, visual change detection, and anagrams failed to identify any sleep-related advantages across these tasks (Brodt et al., 2018). Only riddle tasks showed a positive effect from incubation. Similar contradictory results were observed in another study comparing the benefits of sleep versus incubation on magic tricks and insight problems (Schönauer et al., 2018). In an intriguing examination aimed at contrasting the benefits of sleep versus wakefulness on solving murder cases within a video game, participants were evaluated on various criteria including reasonableness, consistency, story recall, fluency, flexibility, originality, and elaboration skills (Hołda et al., 2020). Findings did not reveal sleep-related benefits for any of the criteria assessed.

From an EEG perspective, non-rem (nREM) sleep dynamics, especially slow-wave sleep (SWS), has long been considered to play an essential role in memory integration (Fogel and Smith, 2006; Wilhelm et al., 2014). SWS is mainly represented by slow oscillations (SO), spindles and sharp-wave ripples. SOs, which are low-frequency oscillations (0.05-4Hz) originating in the cortex (Wilhelm et al., 2014), reflect a back-and-forth between hyper-polarized down-states and depolarized neuronal up-states (Steriade et al., 1993). The up-phase of the SO, characterized by neuronal depolarization, triggers thalamo-cortical spindles, brief oscillations at 9-16 Hz (Steriade, 2006), strongly associated with reactivation (Rasch and Born, 2013). Intriguingly, precise closed-loop TMR (CL-TMR), where cues were delivered at specific SO phases, has revealed distinct impacts on behavioural performance associated with the up and down states of the SO (Shimizu et al., 2018; Göldi et al., 2019). These beneficial effects are believed to arise from more effective reactivation during that particular phase of the oscillation (Rasch and Born, 2013). This, combined with the naturally enhanced synchronization of neural firing during up-states (Vyazovskiy et al., 2009), heightens the likelihood of memory consolidation. An intriguing explanation emerged from a study indicating a positive impact of cueing during the up-phase of slow oscillations on increasing spindle occurrence, which in turn is linked to a reduced rate of forgetting (Ngo and Staresina, 2022).

Meanwhile, numerous findings revealed that neuronal firing sequences expressed during encoding would be reinstated in subsequent periods of sleep (Wilson and McNaughton, 1994) or that reactivation of learning-related brain regions during post-encoding sleep (Maquet et al., 2000; Peigneux et al., 2003) would predict subsequent post-sleep performance improvement (Peigneux et al., 2004; Yotsumoto et al., 2009). On that basis, the hypothesis whereby consolidation could result from neural replay, a key-mechanism of spontaneous reactivation of neural networks engaged during wakefulness emerged (Buzsáki, 1989; Rudoy et al., 1997; Diekelmann and Born, 2010; Paller et al., 2021). Based on the idea of replay, a promising technique known as "Targeted Memory Reactivation" (TMR) was proposed and applied to intentionally trigger reactivation and thus, promote neuronal reactivations and consequently enhance sleep-related benefits. A typical TMR paradigm comprises of three main steps: (1) Encoding of sensory-cued materials, olfactory (Rasch and al., 2007) or more often auditory (Rudoy and al., 2009), during wakefulness. (2) During sleep, the same cue is presented to promote reactivation of the neurons engaged during encoding. (3) Recall accuracy is assessed by comparing the cued and non-cued materials.

Cueing benefits during SWS were found in numerous studies (Rasch et al., 2007; Rudoy et al., 2009; Fuentemilla et al., 2013; Cairney et al., 2014). In a SRTT study where participants were asked to learn motor sequences, TMR during SWS and wake revealed subsequent cueing benefits during sleep whereas TMR during wake resulted in a poor percentage of motor performance improvement that did not significantly differ from the absence of TMR (Cousins et al., 2014). In a face recognition study, TMR application during SWS revealed subsequent recognition benefits conditionally upon undisturbed sleep (Whitmore et al., 2022). Finally, a world-recall sleep study revealed cueing benefits during SWS depending on the phase of stimulation, with an increase of performance but only when stimulation occurred on the up-phase of the SO (Göldi et al., 2019). In line with this study, a recent one that aimed to further knowledge about the SO up-state versus down-state TMR cueing application during SWS (Santamaria et al., 2023) revealed significant and positive immediate TI benefits after TMR application at SO up-phase, that were shown to persist over two weeks. However, in a study comparing the benefits of sleep versus wakefulness in the first

experiment and exploring TMR benefits during SWS versus REM sleep versus wakefulness in a subsequent phase, a significant benefit was found for sleep compared to wakefulness in issue-solving scores. Yet, regardless of the sleep stage cued, no benefits from TMR were identified concerning issue-solving (Beijamini et al., 2021).

In the field of memory integration, an increasing interest about gamma oscillations, from a physiological perspective, brought several reasons to believe that synchronized activity in the gamma-frequency band should have a role in encoding long-term memory through the modification of synaptic connections (Jensen et al., 2007). Indeed, it has been demonstrated that the timing of synaptic discharges, with respect to the phase of ongoing gamma-frequency oscillation, modulates synaptic plasticity (Wespatat et al., 2004). This could be explained by an increase in plasticity when a synaptic discharge coincides with depolarization provided by a peak in the gamma-frequency cycle. Whereas there are few animal studies exploring gamma-frequency activity in paradigms of long-term memory, the relationship between long-term memory and gamma-frequency activity has been supported by several experimental studies in humans. Subsequent memory paradigms using EEG, MEG and iEEG recordings have shown that gamma-frequency activity during encoding predicts recognition of previously encoded items and successful formation of long-term memory (Sederberg et al., 2003; Gruber et al., 2004; Osipova et al., 2006).

Interestingly, gamma frequency has been shown to be coupled with SO (Steriade et al., 1996; Grenier et al., 2001). These experiments demonstrated that gamma oscillations occur preferentially over the active component of the slow wave ("UP" state) characterized by rhythmic cycles of synaptically mediated depolarization and disappear during the hyperpolarizing phase ("DOWN" state). A recent study with microelectrode LFPs in the human cortex has confirmed that gamma oscillations are strongly expressed during SWS and are reliably associated with a marked increase in local cellular discharges, suggesting that they were associated with cortical UP states (Dalal et al., 2010; Le Van Quyen et al., 2010). Nevertheless, although activities in the gamma-range have been observed at the scalp level during a variety of cognitive tasks

(Jerbi et al., 2009), evidences of a phasic expression of gamma activities during SWS in human macroscopic EEG recordings is challenging (Valderrama et al., 2012).

Although sleep research about TMR during SWS and cognitive flexibility provided convincing findings about potential benefits, the exact conditions whereby applying TMR could promote transitive inference abilities, in terms of phase-preference, timing or duration, is still unclear. Building on this, the present study aims to further knowledge about TMR sleep's role in transitive inference emerging at short and long-term. As a second objective, this study aims to investigate the EEG dynamics during SWS after learning to improve the comprehension about how gamma oscillations, at lesser extent sigma oscillations and their phase-coupling with SO are implied in memory integration. For that purpose, 20 participants were recruited and tested in a transitive inference protocol at short (12 hours after sleep) and long-term (a week after sleep). The behavioural hypothesis assumes a higher accuracy after TMR application compared to a control situation irrespective of the time (immediate or delayed). Secondly, TMR is assumed to increase the modulation index (MI), main coefficient of coupling strength between a phase and a specific amplitude. Finally, the MI is expected to correlated with short and long-term accuracy.

2 - Methods

2.1 - Participants

Twenty healthy students (14 females) from Cardiff University, all right-handed and between 18 and 30 (21 ± 1.8) were enrolled in the present study. None of them was shown to express sleep disorders (Table 1) (screened by the Insomnia Severity Index) (Morin, 1993), vision or hearing problem. None of the participants was taking any medication at the time of the experiment and none had a history of any neurological or psychiatric disorders. Based on the anamnestic data collection (cf. Supplementary 1), participants did not report any clinical level of anxiety or depression (screened by the Hospital Anxiety and Depression scale) (Zigmond et Snaith, 1983). Only two

participants reached a HAD anxiety score higher than 10, considered as a "moderate" threshold. The degree of insomnia has been checked by the index of severity insomnia (ISI) scale, a self-rated questionnaire that comprises of 7 questions and for which the score varies from 0 to 28 where higher scores are associated with higher levels of insomnia. For the purpose of this study, the threshold of 14 was chosen as it refers to the subthreshold category of people suffering from insomnia disorder (before the moderate stage). The HAD is also a self-rated questionnaire that comprises of 14 items that range from 0 to 3 for a total of 21. The 14 items are equally divided into 2 sets of questions designed to evaluate anxious or depressive symptoms. For the purpose of the study, participants had to reach a score lower than 7, which refers to the absence of symptomatology. From the day before the experiment to the learning session, the participants were instructed to abstain from caffeine or alcohol. The present study was approved by the internal review board of the University of Cardiff and all the participants gave written informed consent before participating. After completion of the experiment, the participants received a 25£ reward.

2.2 - Items and sounds presentation

The items comprised of 16 pictures of imaginary objects, divided into 2 series hierarchically ordered (e.g., item A > item B >...n) (**Figure 1d**). Hence, from each series, 7 premise pairs (PP) and 21 inference pairs were created. Among these pairs, the anchors (pairs comprising of A and/or H) were excluded from the final analysis because of the presence of the first and last item within them. This decision was motivated by the fact that since the first and the last items are respectively always dominant and submissive, the pairs they are part of are easier to remember. TMR was designed by using 8 sounds of 3 seconds visually related to the items (e.g., a squishy sound for a "squeeze ball"). From these sounds, shorter versions of 200ms were created to be used during the night for the stimulation. The longer versions were used during training phase before sleep to recognize and associate the correct item with its correct sound.

2.3 - Presentation of the EEG setup and the channels

EEG during sleep was recorded using 14 passive electrodes (Brain Vision). Two supplementary electrodes were placed 1 cm left and 1 cm below left eye and 1cm right and 1 cm above the right one to record the EOG. EMG was recorded using two electrodes from each side of the chin. Continuous brain activity was recorded using the international 10-20 locations. Fp1/2, F3/4, Fz, C3/4, Cz, P3/4, Pz, O1/2 and Oz were amplified with a 0.1-200 Hz bandpass, the impedance was kept below 10KΩ and the sampling rate was set to 500Hz. The initial reference chosen was the average between the left and right mastoids. Sleep stages were visually identified offline according to the standard American Academy of Sleep Medicine (ASSM) criteria (Berry and al., 2015). A second sleep scoring process was applied as a comparison measure using the automatic sleep scoring algorithm YASA from Python (Vallat and Walker, 2021).

2.4 - EEG pre-processing and creation of epochs

Datasets were extracted from participants Brain Vision folders. EEG preprocessing was performed using EEGLAB (version 2022.0) toolbox from MATLAB. After the import of channel location, the left and right EOG channels were removed. The data were down sampled to 256Hz. A high-pass filter at 0.5 and a low-pass filter at 40 Hz was applied. Re-referencing was performed using Cz channel. The data was segmented into epochs of 4 seconds starting 1000 Ms before stimulus onset and 3000 Ms after. Each trial was visually inspected and those that contained artifacts were manually removed. On that basis, two conditions were created, namely a "control" and "TMR" one. The condition "control" referred to the SWS portions that did not receive TMR stimulations while "TMR" condition referred to the portions of SWS sleep for which the TMR cueing sounds were applied. Finally, independent component analysis was performed to detect and remove electrodes for which brain signal would be impacted by unwanted artifacts and noise, such as eye movements, muscle activity, or electrocardiographic signals.

2.5 - EEG analysis

After being decomposed into epochs of 4 seconds, the EEG datasets were analyzed to extract the average time-frequency of each condition. The results were statistically compared to detect frequency of interests (delta, spindle and gamma range) susceptible to emerge from the TMR condition. On that basis, a PAC analysis was performed to detect coupling between the delta phase (0.5-4 Hz), spindle activity (13-15Hz) and the gamma amplitude (30-40 Hz). PAC strength was quantified by extracting the modulation index (MI). MI is a robust and reliable marker of coupling that ranges from 0 to 1, where higher coefficients are associated with a stronger coupling.

2.5.1 - Time frequency

Time-frequency analysis was performed using EEGLAB study while phase amplitude coupling (PAC) and epoch analysis were performed using Python. MNE package was used to import, visualize and analyze EEG, matplotlib.pyplot, SciPy and Tensorpac were used to plot the comodulograms, calculate the modulation index (MI) and perform the epochs t-test comparisons. Time-frequency event-related spectral perturbation (ERSP) was performed using EEGLAB study toolbox from MATLAB. The oscillatory power was obtain using a continuous wavelet transformation (Complex Morlet Waveform, 3 0.8 cycles). Concretely, the wavelet used to measure the amount and phase of the data in each successive, overlapping time window started with a 3 cycles wavelet (Hanning-tapered window applied). Then, the number of cycles in the wavelets used for higher frequencies expanded to reach 20% (1 minus 0.8) of the number of cycles in the equivalent FFT window at its highest frequency. The cycle number was chosen to propose a trade-off between a high frequency resolution and time resolution, as higher cycles tend to respectively increase the frequency and decrease the time resolution. Range of frequency was set to 0.5 to 40 Hz, resulting in a range of frequency analyzed from 3Hz to 40 Hz. Significant differences were performed with a permutation-based t-test with multiple comparison correction, n = 1000 randomizations and a statistical threshold set to 0.05.

2.5.2 - Phase-amplitude coupling (PAC) analysis and modulation index (MI)

Phase-amplitude analysis (PAC) was performed with the package Tensorpac from Python in a three-steps process. The phase and amplitude range chosen were respectively 1-10 Hz and 1-40 Hz. First, the Tort PAC method (Tort et al., 2008; 2010) was chosen to compute PAC, as this approach is known to exhibit a robust tolerance to noise and sensitivity to modulation width (Kramer et al., 2008; Amiri et al., 2016). Secondly, a surrogate computation using swap amplitude time blocks was performed. Concretely, amplitude values were shuffled within time blocks across trials. Using this approach helped to preserve the trial structure of the datasets for further analysis (significant amplitude t-test permutation by epoch). Moreover, it also provided a conservative estimate of PAC. As a final step analysis, a correction was applied using the dynamic definition method. Concretely, this method aimed to dynamically define frequency pairs based on the data characteristics or statistical criteria. It is a flexible method that tends to adapt the properties of the dataset and provides for a strong ability to capture unexpected or nuanced couplings.

2.6 - Experimental procedure

The study was designed with Psychopy ©. The global procedure comprised of 3 sessions all occurring in the laboratory (**Figure 1c**): (1) a learning-session before sleep where participants were trained on premise pairs and sound-item association, (2) a testing session around 10 to 12 hours following the last learning session and that contained a full night of sleep where they were tested on the premise and inference pairs and (3) a follow-up seven days after to assess long-term memory changes across time. All the sessions were performed on 24’ inches screen monitors. Participants arrived around 7PM in the laboratory for the first session. The session started with a Karolinska sleep scale (KSS) screening form to check their level of alertness. None of them reported high degree of drowsiness (See. supplementary 2).

After they were presented the global task EEG wire-up procedure, the session started

with a short presentation of the 16 items (2 series of 8 items). Following this, each item was presented again but paired with a sound of 3 sec. duration. After they were presented each association twice, the participants were presented a sound only. After 1.5 sec, a randomized presentation of 3 pictures comprising of the correct item and two distractors were displayed. The participants were asked to press left, up or right arrow to select the correct sound/item combination. After each trial, feedback with the correct item combination (sound + item) was presented. The training was followed by two testing sessions, the first one with the long sound versions, and the last one with the short versions. For each of the them, the accuracy required to pass the sound/item association was 100%.

The learning session started with the presentation of the premise pairs (Figure 1b). Each pair was presented alone for 2.5 seconds and followed by a fixation cross for 1.5 sec. (Figure 1c, 1d). The sequence was repeated twice. The participants were instructed to focus on the pairs and try to remember them. In a second time, the pairs were presented again in a top/down order and in correct and reverse order (e.g., A/B and later B/A). Each pair was associated with a little smiley and question mark on the right (Figure 1c). The participants were instructed to press "UP" or "DOWN" key to find by trial-error reinforcement which item from the pair could hide a smiley, without time-limit response. Using this procedure help them to learn the hierarchical relationship between the premise pairs but without being aware of it. Each pair was presented in a pseudo-randomized order so that the last item from a pair could not precede or follow the first item of the next pair (e.g., C-B; BC). Depending on the correctness of the answer given, the participants were given feedback that took the shape of a yellow happy or red angry smiley. For each trial, the feedback was associated with the correct response that comprised of the correct choice and the sound associated with each item. The participants were instructed to reach at least 80% of accuracy twice in a row or before 10 attempts. After a distraction task where the participants were shown a cooking video tutorial, the testing session started but without feedback (**Figure 1c**). Excepted a different order of presentation and the absence of feedback, the procedure was the same as well as the score of accuracy to reach to complete the task.

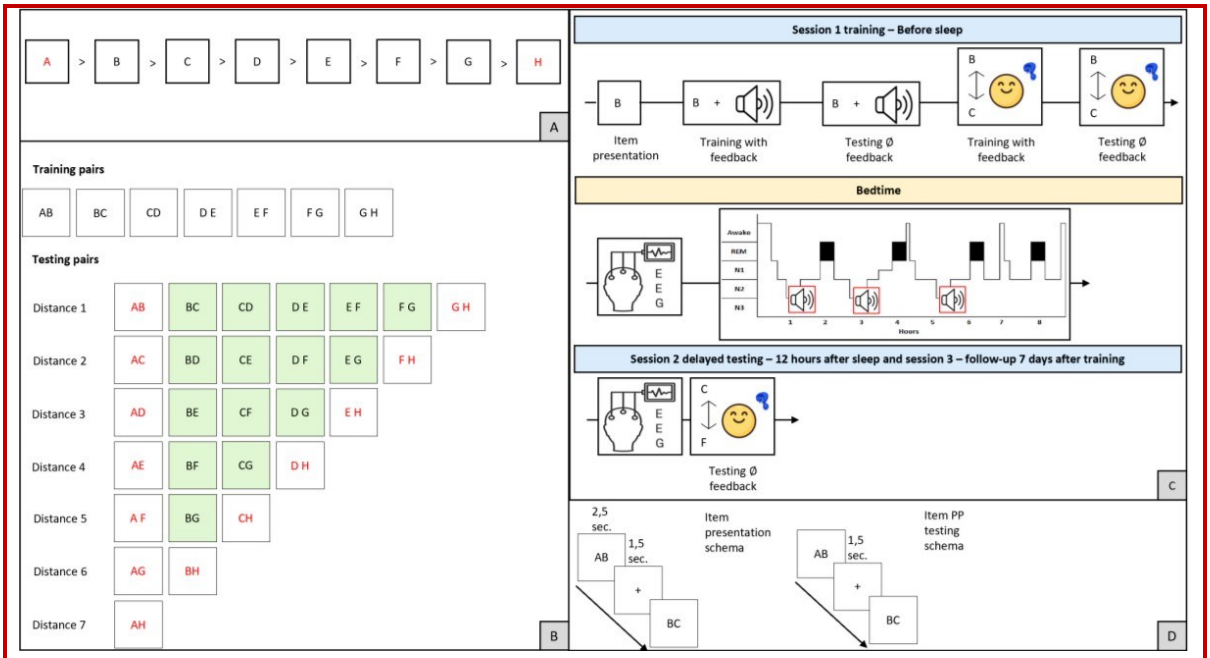


Figure 1: (**a**) Schematic representation of a series of objects. The red items (A and H) are called "anchors" items and were removed from the final data analysis. (**b**) Presentation of the premise and inference pairs. Probe pairs with a green background were used for data analysis whereas the red ones (anchors) were excluded as the first and last pairs are respectively always dominant or submissive. (**c**) Detailed representation of the sessions. The session comprised of an item presentation, the sound/pair association training and testing with long (3sec) and short (200ms) sound versions. During bedtime, cueing sound were presented during SWS for a total of 80 sound presentations. (**d**) Schematic representation of a trial. The presentation of each item is always top/down and the participant is instructed to press UP or DOWN key to select which item is supposed to "cover" a happy smiley.

Figure adapted from Jensen and al., 2019 (Figure 1)

After the completion of the learning session that took approximately 1 hour, the participants were given a break time in the lab bedroom and for which they were allowed to spend time on a quiet activity until the wire-up started. The wire-up time was adapted to fit with participant's usual bedtime, with a limit around 10.30PM. Before the wire-up session started, the participants were given a global explanation about the procedure and the global security process. During each overnight, two experimenters were presented in the sleep lab, available at any time. For that purpose, the participants were given an alarm button-box linked to a speaker in the control room with whom they had the possibility to call the experimenters. After a global explanation of the wire-up procedure, it started with gel skin-allergy test of 5 min, followed by a manual measure of electrode placement and the placement itself. Finally, a wake-up time between 7 and 8.30AM was decided with the participants. During sleep, TMR was applied with the short sound versions of 200ms during SWS

using a semi-automated algorithm detection associated with a pink noise to attenuate the impact of the sound and thus prevent from potential awakening. Concretely, brain activity was monitored in the control room while the main experimenter stayed awake the full night to prevent for any potential issues (cap removal from the participant, reference loss signal…) and activate the TMR program. Specifically, the program was manually launched after the detection of SWS episodes. On that basis, an algorithm designed by a member of the NaPS lab was applied to detect the peaks and throughs of slow-oscillations and thus apply TMR. After each SWS episode, the program was manually turned-off. The TMR program ended after each sound was repeated 18 times. The number of repetitions was decided as a trade-off between the number of sound presentations required to optimize TMR application (based on pilots and former experiments in the lab) and the time needed for this application.

The session 2 started around 10 hours after the participants started to sleep (**Figure 1c**). Participant were given a KSS screening questionnaire to assess their level of alertness. After the electrode removal, they were given the same instructions as during the training session, namely, guessing which item among the pair presented would hide the smiley. However, this session comprised of not only premise but also inference pairs, namely pairs made of combination of items never presented before (**Figure 1c**). These pairs were varying in distance degrees (**Figure 1b**), for a total of 10 premise and 20 inference pairs (e.g., AB; BA for the premise pairs or BD; DB for the inference pairs). The testing phase was repeated 3 times, always with a different pair ordering.

A week after the session 2, participants were asked to repeat the same sequence. For the session 3, the pairs were also presented in a different order top/down and reversed.

2.7 - Calculation of accuracy

In order to account for variability among participants, the global average across trials was used, even though every participant achieved the required 80% accuracy

threshold to pass Session 1. Additionally, in the analysis, anchor pairs were excluded, and only probe pairs were considered for calculating accuracy. Anchor pairs, which consist of the first or last item in the hierarchy, were omitted because they tend to be easier to remember due to their consistent dominance or submissiveness.

2.8 - Selection of features of interest

The data analysis was preceded by a computational detection of features of interest. This process aimed to extract useful information from large data sets and avoid noisy features. The computational approach was a wrapper method, where a global model was calculated and trained based on the features from the dataset. Depending on their ability to explain the variance of the computed model, the features are saved or removed from the model by backward elimination. For that purpose, the method BORUTA was chosen (**see Prabhakaran, 2017 for detailed explanations about BORUTA application with Rstudio**). BORUTA is a feature selection algorithm used in machine learning to identify the most important features for a given model. It operates by iteratively comparing the importance of real features with that of random features (shadows). This approach is based on the concept of random forest, which aims to capture the important features that can explain a particular outcome. The algorithm consists of two steps:

(**1**) The dataset is duplicated and a random forest classifier is trained to detect the important features by assigning a score for the mean decrease in impurity for each feature. A high score is associated with high importance. Three categories are formed. The "shadow min" includes the features with a low importance score, the "shadow mean" includes the features that are close to chance. Finally, the "shadow max" includes the features with high importance.

(**2**) The algorithm compares the importance of the duplicated features with that of the real dataset. After a certain number of iterations, a real feature is retained if it has a higher z-score than its shadow.

The importance score for each feature in the BORUTA analysis is derived from the importance measure provided by a random forest model. Random forest models, in

turn, provide importance scores for each feature based on how much they improve the model's performance when they are included. A positive importance score indicates that the feature contributes positively to the predictive performance of the model. The higher the score, the more important the feature is deemed to be. A negative importance score implies that the feature detracts from the model's performance. This might seem counterintuitive, but it can occur for several reasons:
1/ The feature might be adding noise to the model, reducing its accuracy.
2/ The feature could be correlated with other features (multicollinearity), leading to unstable importance scores.
3/ The feature might interact poorly with other features (interaction effect) in a way that negatively impacts the model's overall performance.

2.9 - Model selection and calculation of parsimony

The parsimony and the quality of the models were assessed with the Mallow Cp (**see Bobbitt, 2021 for detailed explanations about Mallow Cp calculation with Rstudio**), a variant of AIC (Akaike Information Criteria) developed by Colin Mallows. Technically, the likelihood of a given model can be increased by adding more parameters. Thus, the more parameters used, the more informative the model. However, because the coefficient used (R^2) is a square, it cannot decrease as more parameters are added, which can improve the explanatory power of a model due to chance rather than the efficiency of its parameters. To limit this bias, the Mallow Cp was applied to assess the fit of the regression models on the basis of the features detected by BORUTA. The main objective here was to detect the most precise and accurate model that would need the lowest number of predictors to reach that precision. Among multiple models available, the one that exhibits the lowest Cp value is the most precise. Mallow Cp is calculated as follows:

Mallow Cp = (SSE_p / MSE_F) - (N - 2P)

. SSE_p = Sum of square errors for the potential model
. MSE_F= Mean square error of the full model
. P = number of predictors. The penalty N-2P represents the cost for a model that incorporate high number of predictors.

This method is consistent with the concept of parsimony, which aims to find a trade-off between the explanatory power of a model and its ease of use.

2.10 - Selection of unbiased effect sizes

The magnitude of the difference between means was described by using the Hedge's g. This effect size is the non-biased equivalent of the Cohen's d but for small sample size (n < 50). The formula used to calculate Hedge's g was:

Hedge g = (M1 - M2/ SD pooled) * (N - 3 / N - 2.25) * ((√N - 2) / N)

. M1 - M2 represent the mean difference.
. SD pooled is the weighted standard deviation

Finally, the adjusted R^2 was used as a coefficient of determination (**see Bobbitt, 2020 for detailed explanations about adjusted R^2 calculation with Rstudio**). This coefficient is consistent with the use of the AIC, as it captures the degree of parsimony of the model used. Technically, a malus is added to the R^2 if a predictor improves the model by less than chance. This process aims to avoid a natural increase in the R^2 value when predictors are added to the model, since the coefficient cannot decrease (a square is always positive). However, the penalty is reduced if a predictor is found to increase model accuracy more than by chance. The adjusted version of the R^2 is always lower than its biased version.

The formula is presented as follows:

Adjusted R^2 = 1 - (1 - R^2) (N - 1) / N - p - 1

. N = sample size
. p = number of predictors

2.11 - Use of robust regressors

Due to the variability of the data observed, the classic ordinary least squares (OLS) estimator used to compute linear regression was associated with a robust regression estimator, the Theil-sen estimator. Instead of relying on every single data point equally

like OLS does, the Theil-Sen estimator calculates the slopes and intercepts from various subgroups formed by combinations of a few data points. For instance, while estimating an intercept, the number of points in each subgroup (denoted as 'p') should be at least as many as the number of features ongoing dealing with, plus one. Once these slopes and intercepts are calculated, the final values are determined as what's called the 'spatial median' of all these different slopes and intercepts.

3 - Results

3.1 - Detection of features of interest

The feature detection with BORUTA aimed to detect features the most susceptible to explain transitive inference performance over time. For that purpose, the anamnestic features, namely KSS (questionnaire measuring the level of alertness), HAD anxiety and depression (self-questionnaire respectively measuring the degree of anxiety and depression) and ISI (self-questionnaire measuring the degree of insomnia) have been assessed, as well as the experimental ones such as the condition (TMR versus control), the session (Session 2 or short-term versus Session 3 or Long-term) or the premise pairs accuracy before sleep. Finally, the neural correlates represented by the modulation index (MI) delta gamma and delta spindle have been taken into account (**Figure 2**).

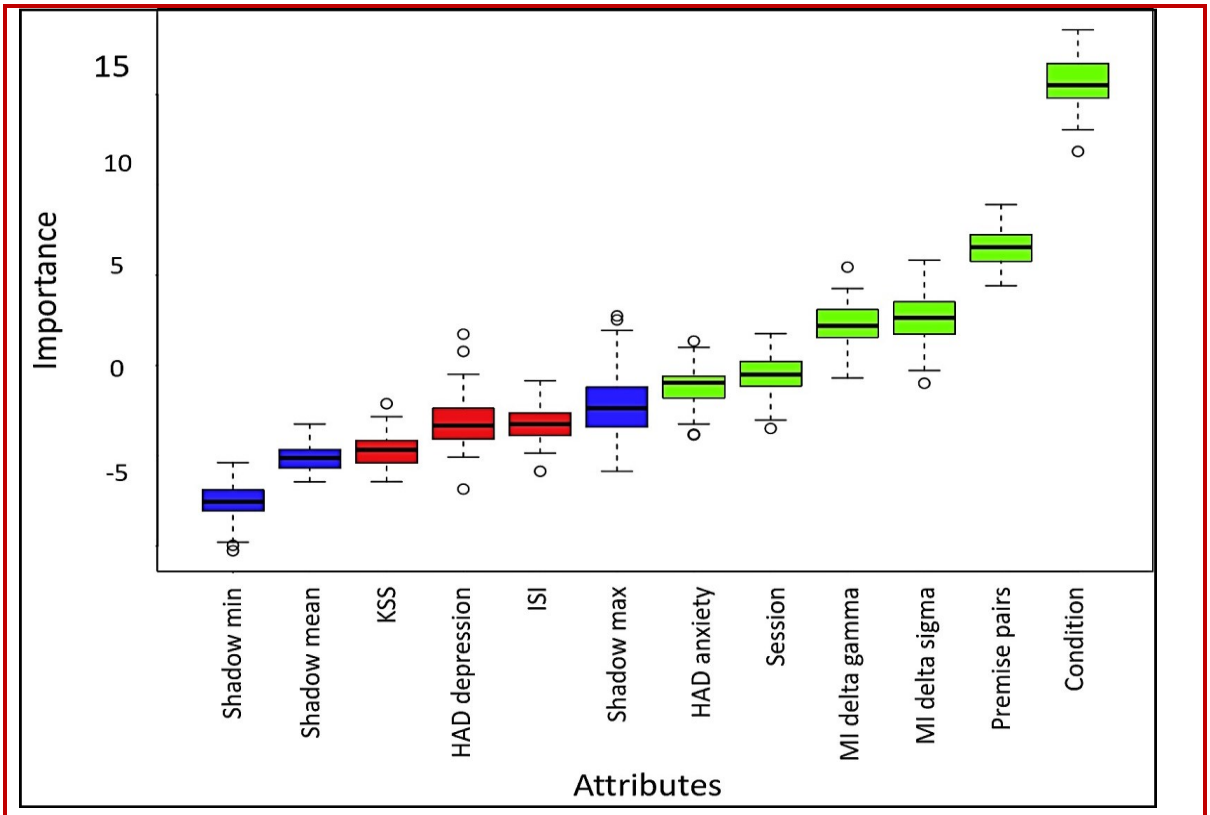


Figure 2: Classification of features of interest for inference pairs, sorted by degree of importance. The classification ended after 32 iterations. The main features detected are the HAD anxiety, the session, the MI delta gamma, delta sigma, the premise pairs accuracy and the condition, each significantly higher than randomness effect represented by the shadows (blue boxplots).

The maximum number of iterations was set to 800. However, only 32 were needed to classify the features, highlighting the robustness and efficiency of the algorithm to distinguish between relevant and irrelevant features. As shown in the figure 2, most of the feature's values were classified above the shadow's min features (randomized or shuffled copies of the original features used for the classification). Among the features that appeared to explain the variability of TI performances, HAD anxiety, the session, the MI delta gamma, delta sigma, the premise pairs accuracy and the condition were ranked as presented. However, a visual inspection of the best features clearly showed that they did not equally explain TI performances. Indeed, with a much higher mean of importance compared to others, and in line with the main assumption, the condition feature appeared and by far, to be the best feature of explanation (**Figure 2**).

3.2 - Comparison of models' parsimony

The feature selected earlier were compiled in multiple models that aimed to explain TI accuracy. The output "accuracy" and the most relevant feature "condition" were used as a baseline model (accuracy ~ condition). On that basis, three more models were built by adding supplementary features of interest, leading to increase the explanatory power of these models but also their level of complexity and potential bias. Building on this, a three-steps model selection procedure, based on the principle of parsimony was performed. The first step aimed to assess the Adjusted R^2 metrics of the models that addressed the issue of overfitting by penalizing for the inclusion of irrelevant predictors. The second step consisted in analyzing the Mallow's Cp that aimed to compare the mean squared error of a model to that of the full model (with all predictors) and penalize for the inclusion of additional predictors that did not significantly improve the model fit. The last step consisted in performing an ANOVA of the selected models to detect for any significant differences in their simplicity and accuracy. The function ols_step_all_possible from the Rstudio package Olsrr was used to compute and test all possible models. The multi-model comparison revealed 31 combinations. On top of these, as shown below (**Figure 3**), the baseline model exhibited a decent adjusted R^2 (Adj. R^2 = 23%) as well as a decent Mallow's Cp metric (M. cp = 24.1). Adding the session condition appeared not only to increase the baseline model performance (Adj. R^2 = 25%) but also its parsimony (M. cp = 22.8).

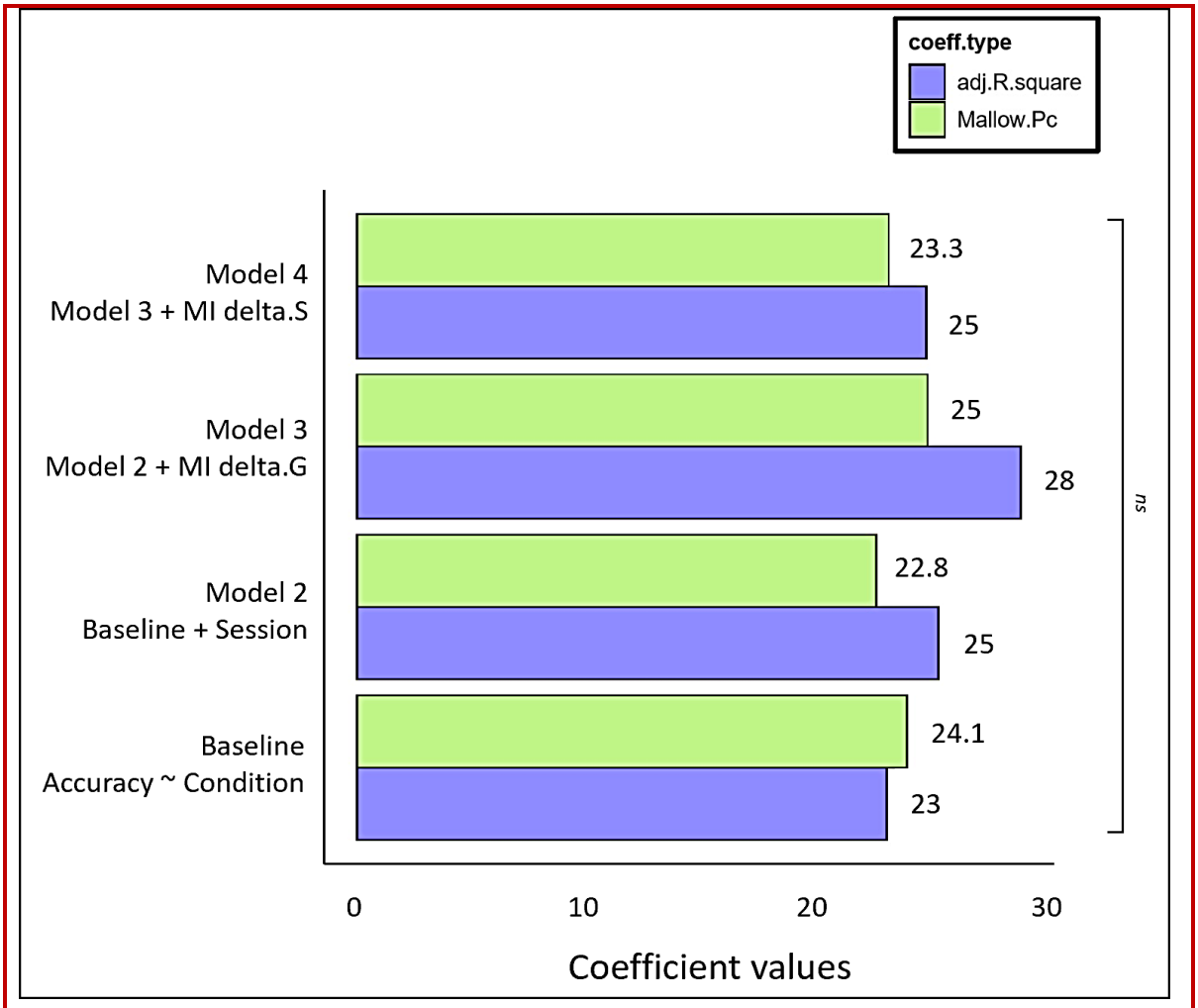


Figure 3: Graphical representation of model comparison between the baseline and the most parsimonious models for inference pairs. For each model, the adj. R^2 and Mallow's Cp were extracted and compared. An association between a small Mallow's Cp value and a high adj. R^2 coefficient is required to detect the most parsimonious and accurate model.

The last 2 models, respectively represented by the delta/gamma coupling and the delta/sigma coupling strength did not appear to strongly improve the model. However, adding these features did not reveal a strong and significant decrease of parsimony. As both MI coupling are source of interest in the present study, the most complex model, namely accuracy ~ condition + session + MI delta/gamma + MI delta/sigma was selected for further analysis. Finally, the ANOVA comparison between models did not reveal any significant differences between model 1 and 2 ($F(1, 77) = 2.69$, $p = 0.105$), the models 1 and 3 ($F(1, 76) = 1.85$, $p = 0.177$) or the models 1 and 4 ($F(1,75) = 0.87$, $p = 0.353$).

3.3 - TMR during SWS promotes long-term TI accuracy

After sleep, comprising of TMR during SWS or no stimulations, participants were tested on their delayed abilities to infer about new item associations 12 hours after learning and after a week (**see methods**). The absolute means for session 2 and 3 are presented **table 1**.

The analysis started with a 2*2 ANOVA to detect whether the session time (session 2 and session 3) by the TMR application (Yes versus No) could predict inference accuracy. The results revealed a condition ($F(1, 76) = 26.38$, $p = 2.1e\text{-}06$) but no session effect ($F(1, 76) = 2.77$, $p = 0.100$) as well as no interactions although close to significance ($F(1, 76) = 3.91$, $p = 0.051$). Overall, the main findings revealed a positive and significant impact of TMR upon TI accuracy at session 2 (**Figure 4**), meaning 12 hours after sleep ($t(19) = 5.29$, $p = 4.17e\text{-}05$, 95% CI [11.69, 27.01]; Hedge's g = 1.68, 95% CI [0.95, 2.41]). However, no significant difference about TI accuracy was found between condition after a week (**Figure 4**) ($t(19) = 1.89$, $p = 0.072$, 95% CI [-0.87, 18.08]; Hedge's g = 0.64, 95% CI [0.003, 1.29]). Overall, TMR appeared to strongly promote TI above chance after sleep compared to control condition. However, further analysis did not reveal any maintain of benefits after a week despite of a higher accuracy for the TMR condition. If the reasons that led to massive delayed decrease of performance for the TMR group (-13%) after a week are unclear, it seems clear that the stable performance without any significant changing dynamics between sessions (+0.02%) for the control group can be explained by the fact that control group did not manage to infer pairs associations above chance at any time of the sessions.

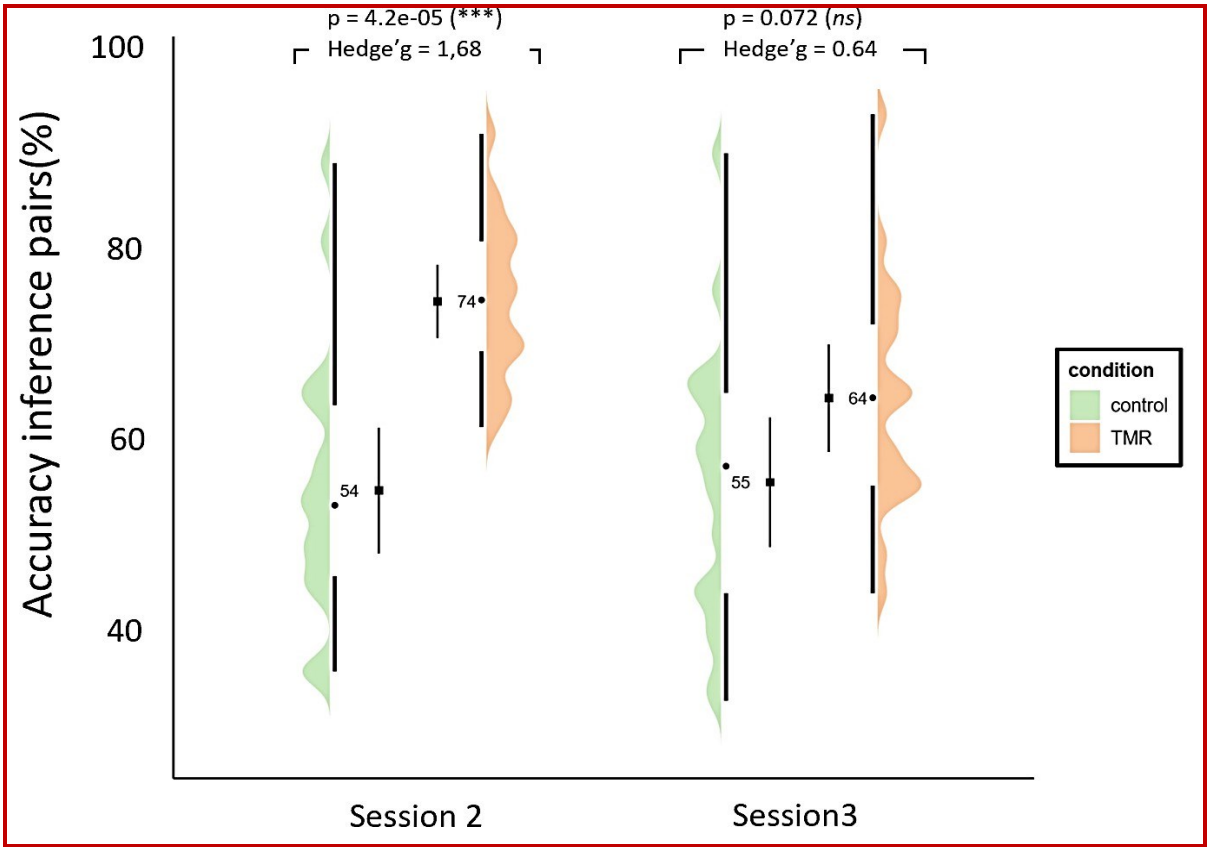


Figure 4: Accuracy for the inference pairs after 12 hours and after 7 days (N = 20 participants per groups). Dots and thick back lines are minimalist boxplot representations. Black squares and numbers are means and error bars are CI. ns = non-significant..

3.4 - EEG neural correlates of TI: time-frequency comparison

The investigation of neural correlates started with a time-frequency analysis of EEG epochs in order to detect any clusters of interest in the delta, sigma and gamma range. For that purpose, a preliminary topographical comparison was performed to select the appropriate channels (**Figure 5**). For that purpose, the brain activity from stimulus onset to 3000ms following stimuli presentation was compared to the baseline, namely the averaged brain activity from 1000ms before stimuli to the stimulus onset period. A cluster-based, two-tailed one-sample permutation test (1,000 randomization and a statistical threshold of 0.05) was performed, revealing F3 and Oz, two channels of interest (**Figure 5c**). Due to the fact that occipital channels are barely involved in the frequency of interest of this study, F3 only was selected.

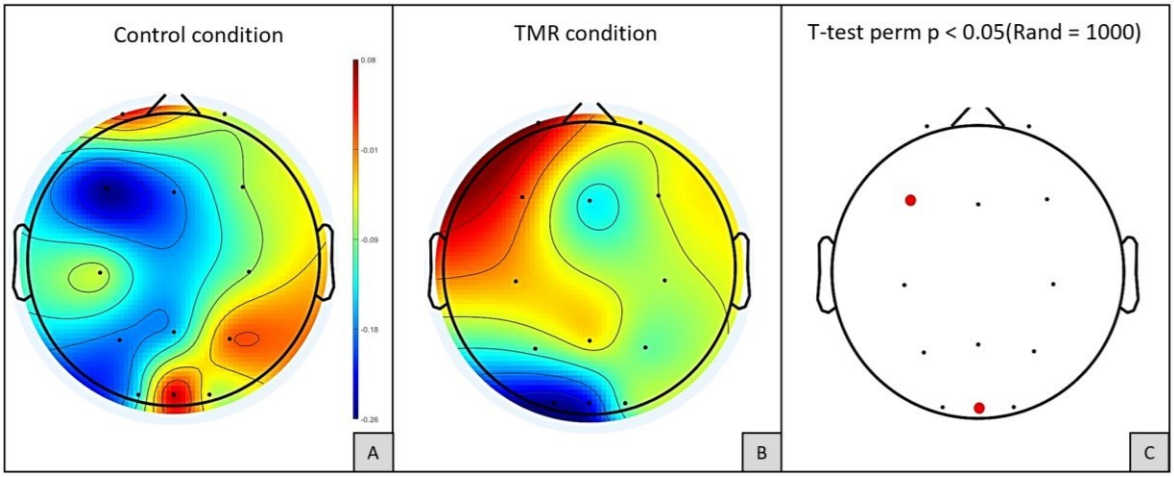


Figure 5: Topographical amplitude changes of brain activity power (μV^2) for control TMR conditions at 1000 ms before stimulus and 3000 ms after stimulus onset. (**a**) Control condition is significantly represented by a parietal and occipital activity in the right hemisphere. (**b**) Brain activity for the TMR condition appears to be driven by frontoparietal regions significantly lateralized in the left hemisphere. (**c**) Permutation t-test between condition revealed F3 (top-left red spot) and Oz (down red spot) as channels of interest.

On that basis, a time-frequency analysis was performed. The cluster-based, two-tailed one-sample permutation test (1,000 randomization and a statistical threshold of 0.05) identified two principal frequency ranges. The control condition (**Figure 6a**) revealed a sigma activity (12-15 Hz) around 15 Hz at 0-100 Ms following stimulus and a low gamma range (25-35 Hz) between 500 and 1000 ms after stimulus onset. The TMR condition revealed a high delta (3-5 Hz) cluster 200 Ms at both sides of the stimulus onset (**Figure 6b**). Moreover, a long range of low-gamma activity (25-35 Hz) from 0 to 2000 Ms after stimulus.

Based on the clusters identified, an Event-related desynchronization/synchronization (ERDS) changes analysis was performed (**Figure 7**) to confirm the impact of TMR upon delta, sigma and gamma frequency over time. A paired sample t-test revealed a non-significant difference for the delta cluster ($t(79) = 0.23$, $p = 0.814$, 95% CI [-0.02, 0.04]; Hedge's $g = 0$, 95% CI [-0.31, 0.31]), the gamma cluster ($t(79) = 0.91$, $p = 0.371$, 95% CI [-0.01, 0.02]; Hedge's $g = 0.04$, 95% CI [-0.27, 0.4]), but a significant difference maintained over time for the sigma cluster ($t(79) = 2.11$, $p = 0.035$, 95% CI [0.01, 0.26]; Hedge's $g = 0.33$, 95% CI [0.02, 0.64]). A reason susceptible to explain the discrepancy between the findings from the time-frequency and ERDS analysis is the degree of sensitivity.

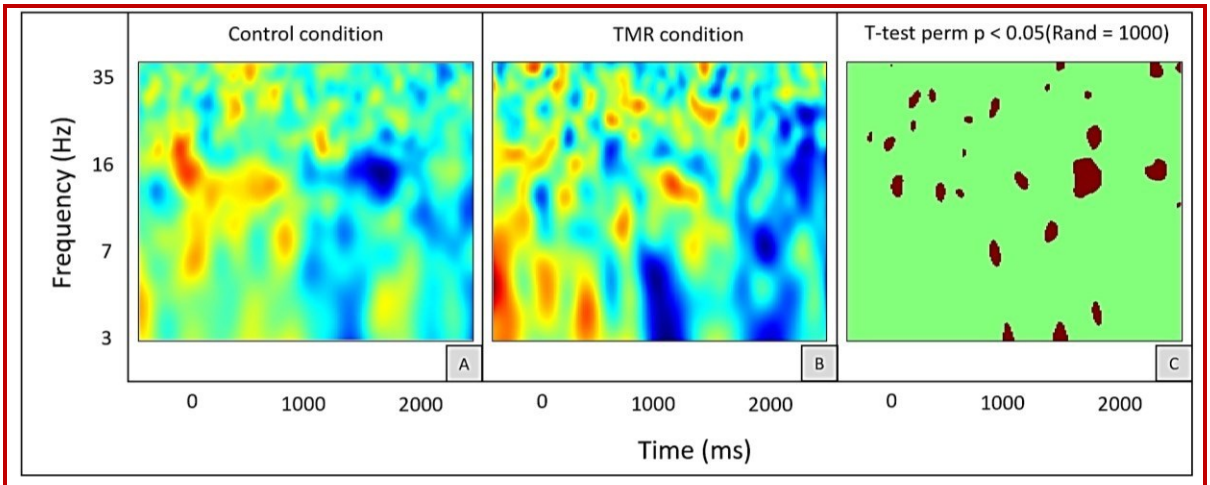


Figure 6: Electrophysiological differences between control and TMR. (a) Control condition reveals an increase of power around 100 ms following stimulus onset in the sigma range. (b) TMR condition appeared to increase the delta (3-5 Hz) and low gamma range (35 Hz). (c) Permutation t-test map between condition. Main changes appeared after stimulus onset. Clusters of significant differences scattered around the stimulus onset were visible in the delta, sigma and low gamma range

Indeed, while time-frequency analysis provides a detailed temporal view of how the power in each frequency band changes, this type of analysis is sensitive to changes in power across time within a specific frequency band. However, ERDS, is less sensitive to rapid changes and may emphasize more sustained changes in power relative to a baseline period. Taken together, these findings suggest a benefit from TMR application in the power increase of delta, sigma and gamma range. These results are in line with the well-known relationship between delta and spindle frequencies, assumed by the active system consolidation (ACS) model, to contribute to the consolidation of declarative memory (Born and Wilhelm, 2012; Rasch and Born, 2013).

Taken together, these findings suggest a benefit from TMR application in the power increase of delta, sigma and gamma range. These results are in line with the well-known relationship between delta and spindle frequencies, assumed by the active system consolidation (ACS) model, to contribute to the consolidation of declarative memory (Born and Wilhelm, 2012; Rasch and Born, 2013). Moreover, the presence of delta and gamma could suggest the presence of rhythmic slow activity (RSA) often coupled with gamma frequency and that can be observed in both humans (Bodizs and al., 2001; Clemens and al., 2009) and rodents (Bland and Whishaw, 1976).

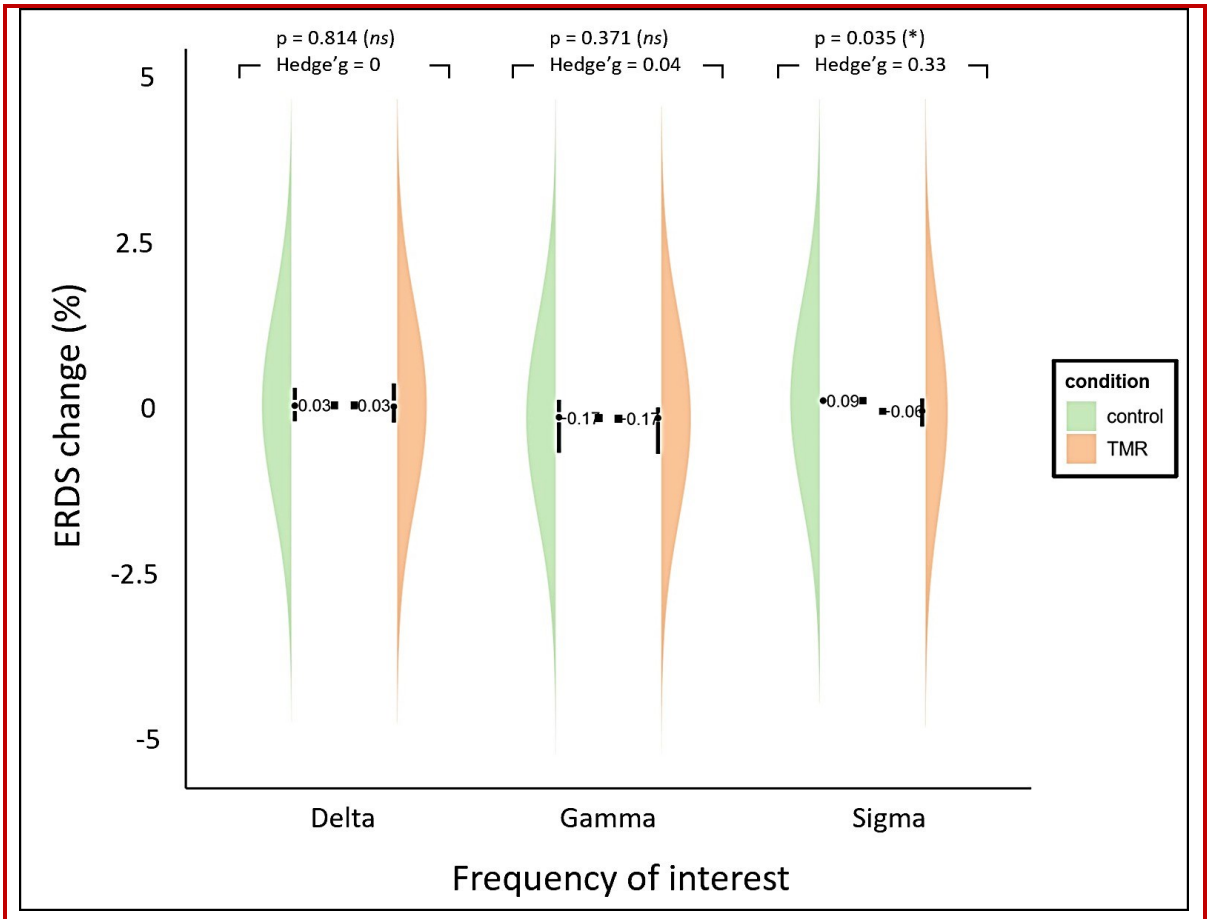


Figure 7: ERDS percentage of power changes for the delta, gamma and sigma clusters (N = 20 participants per groups). Dots and thick back lines are minimalist boxplot representations. Black squares and numbers are means and error bars are CI. ns = non-significant.

Although RSA implication is unclear, multiple findings suggest a crucial role in memory integration (Bódizs and al., 2001; Nuñez and Buño, 2021). A summary of the results is presented **Table 1**.

3.5 - Theta-gamma PAC modulated by TMR

Since delta and gamma frequencies have been shown to be coupled together (Steriade and al., 1996; Grenier and al., 2001), as well as delta and spindles (Born and Wilhelm, 2012; Rasch and Born, 2013), the next part of the investigation aimed to extract the strength of coupling between delta/gamma and delta/sigma frequencies (**Figure 8**) to compare the action of TMR upon their index of modulation (MI) (**Figure 9**). For that purpose, the delta phase (1-4 Hz) on sigma (13-15 Hz) and low-gamma (30-40 Hz) was extracted from each participant's brain activity during sleep following premise

learning and averaged by conditions.

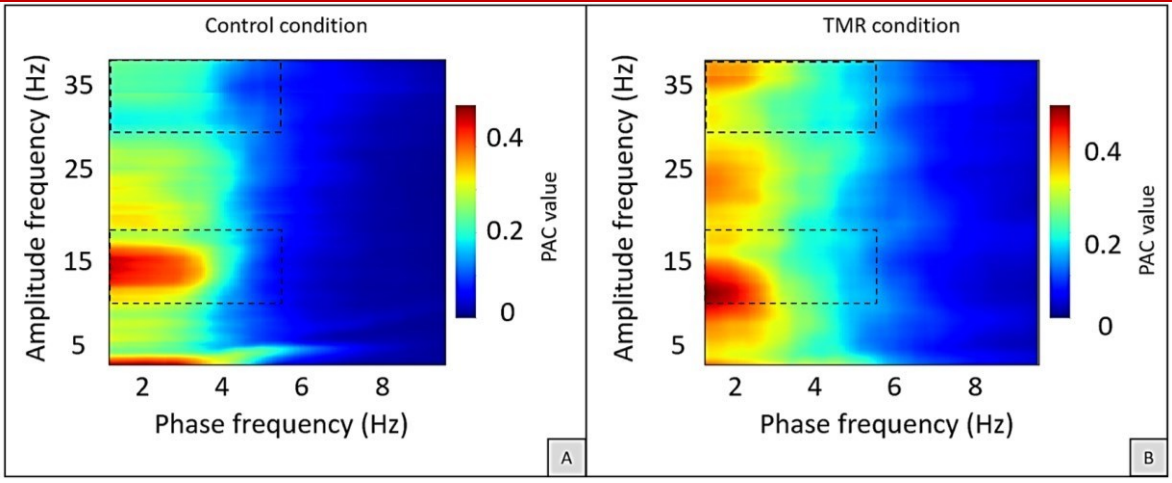


Figure 8: PAC representation averaged between participants. (**a**) Cross frequency spectrogram for the control group reveals a delta (2-4 Hz) phase-locked with a large sigma (13-15 Hz), beta (15-17 Hz) but no low gamma range (32-40 Hz). (**b**) After TMR application, coupling dynamics tends to decrease for the delta and sigma frequencies but to increase in the low delta and gamma range. Modulation index between phase and amplitude is averaged by participants. Black square represented by the dotted lines represents the region of interest.

PAC values were computed in a three-step process (see methods) using Python Tensorpac package that comprised the Tort PAC approach, a swap amplitude time block surrogate computation and finally a dynamic definition correction. A visual inspection of the comodulogram from the control condition (**Figure 8a**) revealed a clear delta phase coupled with the sigma frequency range corresponding to the spindle activity (13-15 Hz) as well as at lesser extent, the low beta range (16-20 Hz). However, the low-gamma range of frequency (top black dotted-line square) did not seem to be coupled with the delta frequencies. Comparatively, a clear delta-gamma coupling was revealed around 35 Hz for the TMR condition (**Figure 8b**). Moreover, and despite of an evident coupling with the sigma amplitude, the strength of coupling appeared much scattered around the range of 13 Hz.

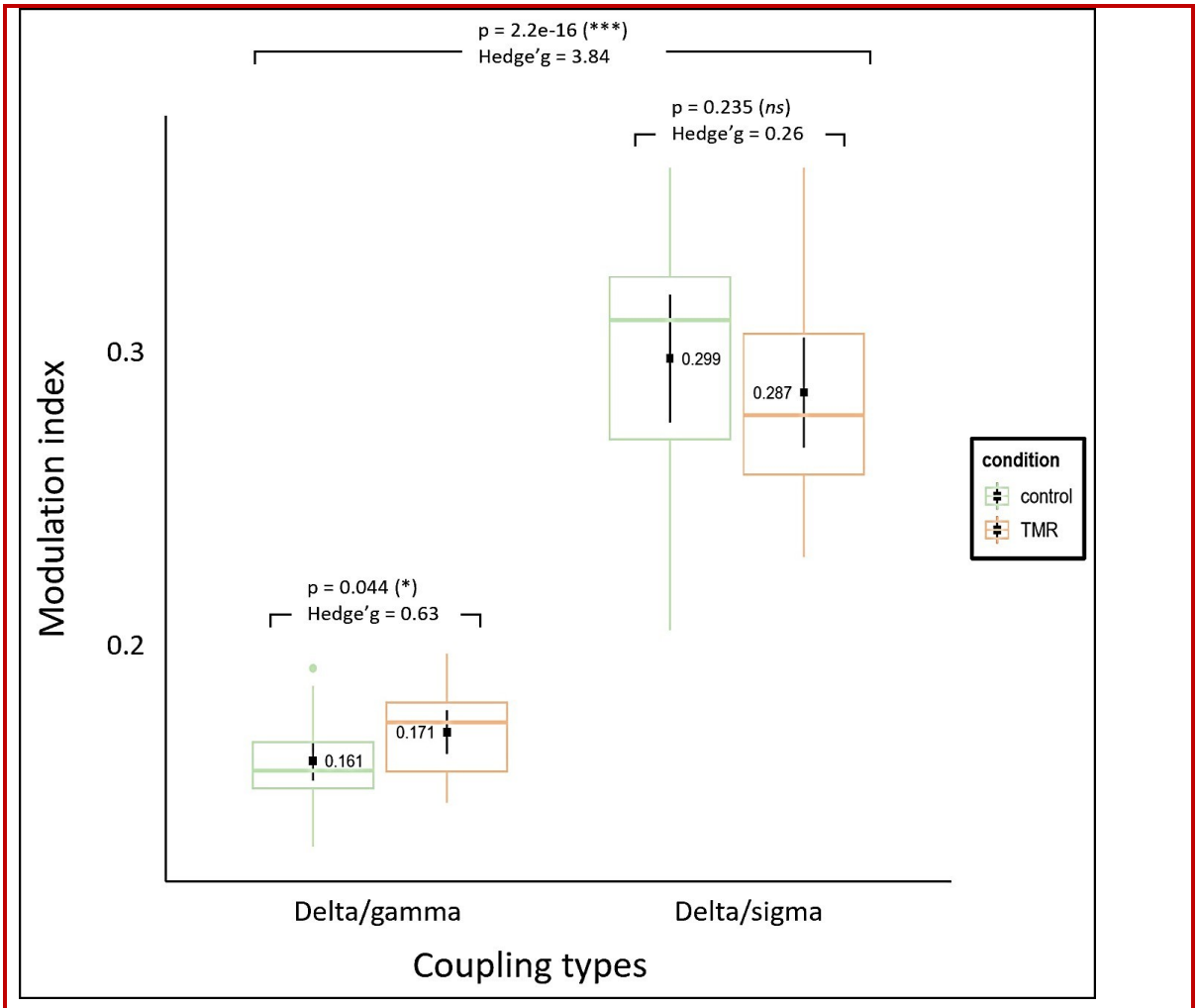


Figure 9: MI representation averaged between participants. Only delta/gamma coupling appeared to be significantly modulated by TMR. Although delta/sigma coupling strength appeared much higher than delta/gamma, a much larger variability can be observed. Black squares and numbers are means and error bars are CI. ns = non-significant.

Building on the findings from the comodulograms from each condition, a 2*2 ANOVA was performed to detect whether the type of coupling (delta/gamma versus delta/sigma) by the TMR application (TMR versus control) could predict the MI coupling. The results revealed a coupling effect ($F(1, 76) = 301.74$, $p = 2.e\text{-}16$) but no condition effect ($F(1, 76) = 0.015$, $p = 0.902$) (**Figure 9**). A paired t-test analysis performed between conditions revealed a small but significant difference between control and TMR for the delta/gamma coupling ($t(19) = 2.14$, $p = 0.044$, 95% CI [-0.02, 0.01]; Hedge's g = 0.63, 95% CI [-0.27, 0.36]) but not for the delta/sigma coupling ($t(19) = 1.22$, $p = 0.235$, 95% CI [-0.08, 0.03]; Hedge's g = 0.26, 95% CI [-0.36, 0.89]).

Overall, PAC analysis revealed an interesting effect of TMR upon the strength of coupling between delta phase and sigma or low-gamma amplitude. Indeed, a higher delta/sigma coupling was observed for the control condition compared to TMR. The TMR condition however, revealed a progressive coupling with the gamma range. Taken together, these findings suggest that TMR application during SWS led to shift the coupling from sigma to low-gamma range. A summary of the results is presented **Table 1**.

3.6 - Delta-gamma/sigma PAC and TMR impact upon transitive inference

At this stage, physiological analysis has shown an impact of TMR during SWS in the strength of coupling between delta and gamma or sigma frequencies. Moreover, at the behavioural level, inference pairs influenced by TMR exhibited a higher accuracy rate, compared to the control condition for which inference pairs were guessed at the chance level. Building on these findings, the last part of the present analysis aimed to assess whether the strength of coupling represented by the modulation index could predict TI accuracy at short and long term. Because of a high degree of variability, the classic linear approach based on the ordinary least squares (OLS) estimator has been associated with the Theil-Sen estimator, much robust against outliers (see methods). Its standout feature is its ability to handle roughly up to 29.3% of corrupted or outlier data points in a simple linear regression scenario. More specifically, Theil-sen estimator finds the 'middle ground' among many slopes and intercepts calculated from different smaller groups of data points, rather than solely relying on all data points equally like OLS.

The preliminary results based on the model accuracy ~ MI + condition + session + coupling_type revealed a significant global effect ($F(4, 155) = 15.09$, $adj.R^2 = 0.26$, $p = 1.94e\text{-}10$). A deeper analysis revealed that the global model accuracy was mainly driven by the condition ($p = 1.96e\text{-}11$) and at lesser extent by the session ($p = 0.021$). Since Theil-sen regression only fits with bivariate models, the global model was split by condition and session, resulting in four different models per coupling types

(delta/gamma and delta/sigma) (**Figure 10, figure 11**). The analysis started with the relationship between the MI delta/gamma coupling and TI accuracy at session 2 and session 3. For each model, Theil-sen regression revealed its robustness against outliers compared to the classic OLS. Relationship at session 2 for the control condition revealed a positive trend with the OLS ($F(1, 18) = 1.52$, $adj.R^2 = 0.06$, $p = 0.232$) (**Figure 10a**).

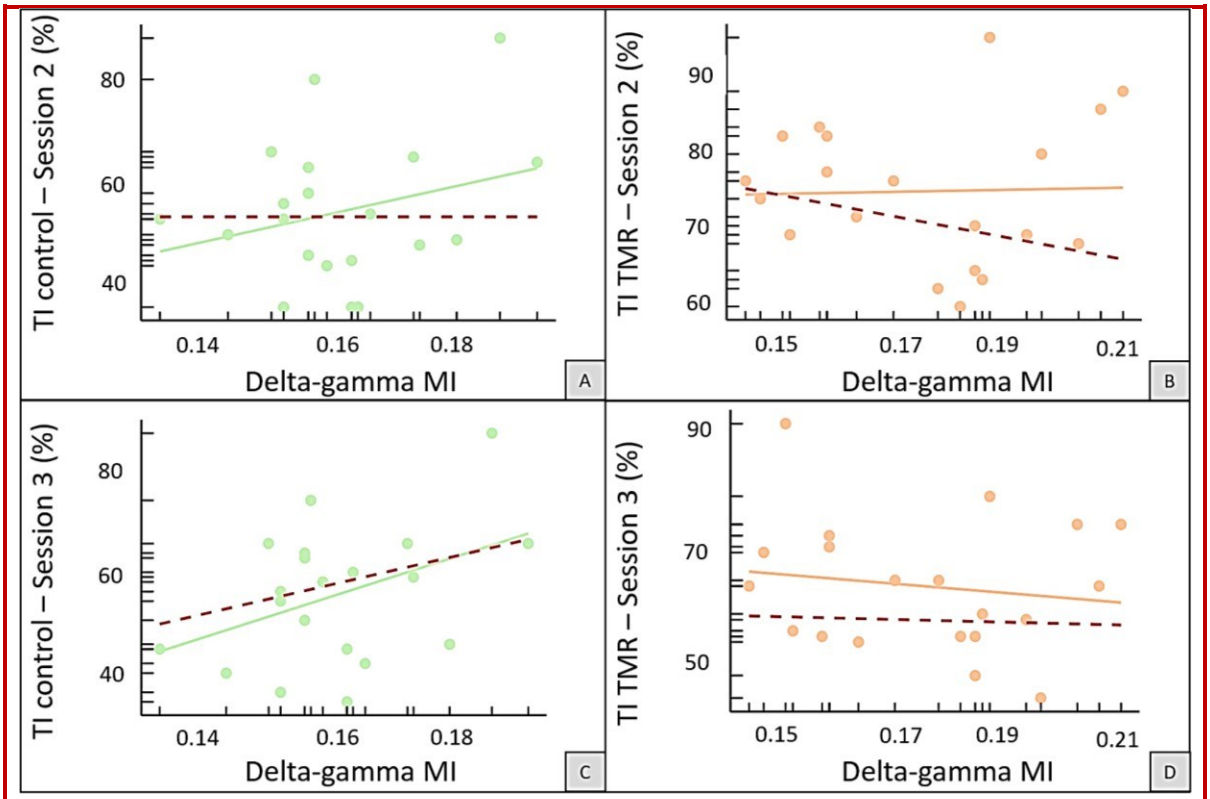


Figure 10: Representation of the relationship between the MI, representing the strength of coupling between delta and gamma frequency, and the transitive inference accuracy per sessions and conditions. Plain and red dashed lines respectively represent the linear (OLS) and Theil-sen estimators. (**a**) Relationship after sleep for the control group. Due to its robustness, the Theil-sen regression revealed the flat relationship between MI and TI accuracy. (**b**) Relationship after sleep for the TMR. The flat trends revealed by OLS goes against the Theil-sen approach that exhibits a negative relationship. (**c**) Relationship at follow-up for the control group. Surprisingly, a positive and significant relationship was found. (**d**) Relationship at follow-up for the TMR group

However, Theil-sen approach managed to detect the real flat trend between the MI and the accuracy (**Figure 10a**) (Pseudo $R^2 = 0$, Theil-sen $p = 0.810$). Similarly diverging findings appeared for the TMR condition (**Figure 10b**). Indeed, while OLS regression suggested a flat trend between MI and accuracy ($F(1, 18) = 0.015$, $adj.R^2 = 0$, $p = 0.901$), surprisingly, Theil-sen revealed a negative relationship (Pseudo $R^2 =$

0, Theil-sen p = 0.143). A similar analysis was performed at follow-up session. Surprisingly, the regression analysis for the control condition revealed a positive and significant relationship for both OLS and Theil-sen regressions (F(1, 18) = 4.539, adj.R^2 = 12, Pseudo R^2 = 13, p = 0.047, Theil-sen p = 0.045) (**Figure 10c**). However, the relationship at follow-up for TMR condition did not reveal significance (F(1, 18) = 0.397, adj.R^2 = 0, Pseudo R^2 = 0, p = 0.536, Theil-sen p = 0.324) (**Figure 10d**).

A similar analysis was performed for the coupling strength between delta/sigma coupling and TI accuracy, at short and long-term interval.

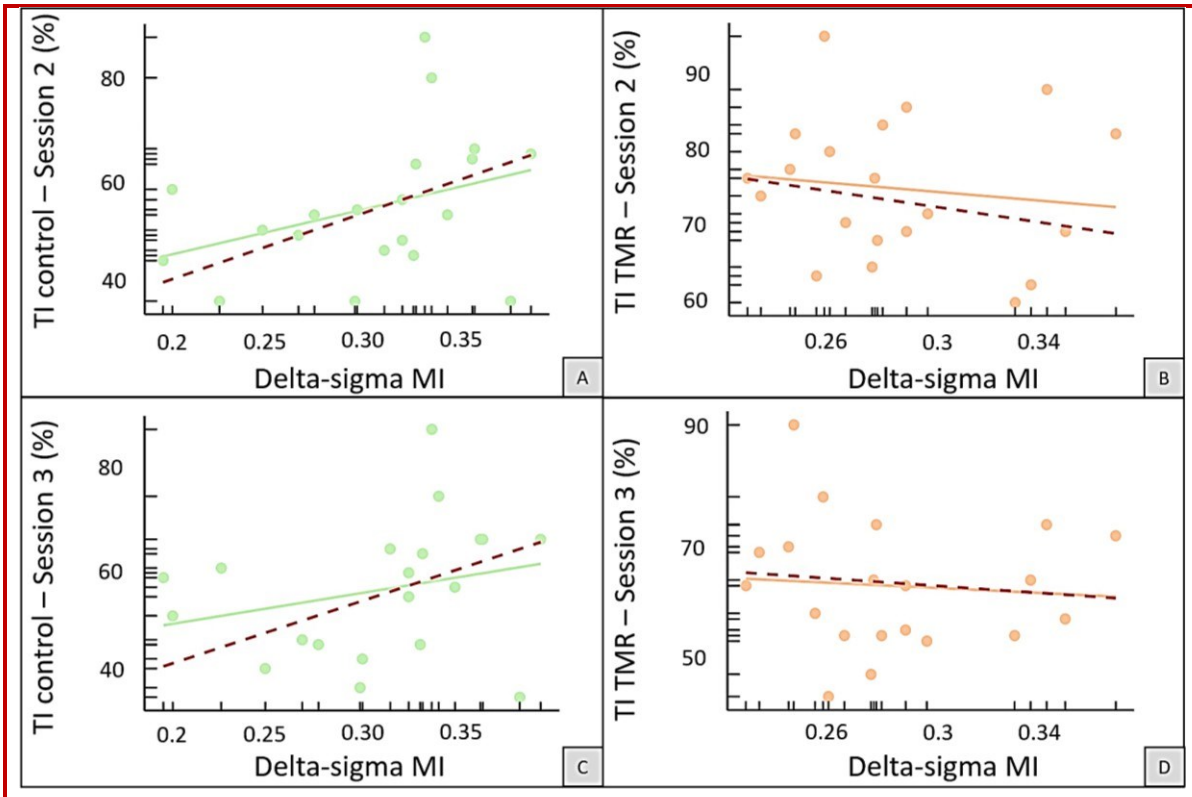


Figure 11: Representation of the relationship between the MI, representing the strength of coupling between delta and sigma frequency, and the transitive inference accuracy per sessions and conditions. Plain and red dashed lines respectively represent the linear (OLS) and Theil-sen estimators. (**a**) Relationship after sleep for the control group. MI significantly correlates with TI accuracy. (**b**) Relationship after sleep for the TMR. In line with the delta/gamma coupling trend, both OLS and Theil-sen approaches exhibit a negative relationship. (**c**) Relationship at follow-up for the control group. Again, a positive and significant relationship was found. (**d**) Relationship at follow-up for the TMR group.

The analysis of the relationship at session 2 for the control group revealed a massive difference between OLS and Theil-sen approach. Indeed, while OLS appeared to

exhibit a positive but non-significant relationship between the MI and the TI accuracy ($F(1, 18) = 2.59$, $adj.R^2 = 0.08$, $p = 0.124$) (**Figure 11a**), Theil-sen revealed not only a positive but also a significant trend (**Figure 11a**) (Pseudo $R^2 = 0.1$, Theil-sen $p = 0.001$). Comparatively, similar findings appeared for both regression models for the TMR condition at short-term, revealing an absence of relationship between the MI and the TI accuracy ($F(1, 18) = 0.295$, $adj.R^2 = 0$, Pseudo $R^2 = 0$, $p = 0.593$, Theil-sen $p = 0.211$) (**Figure 11b**). Relationship at follow-up for the control condition revealed again a massive difference in terms of degree of relationship and significance (**Figure 11c**). Indeed, the absence of relationship and significance from the OLS ($F(1, 18) = 1.30$, $adj.R^2 = 0.02$, $p = 0.269$) went against the decent degree of relationship and the strong significance raised by Theil-sen (Pseudo $R^2 = 0.13$, Theil-sen $p = 0.0004$). Finally, the follow-up session for the TMR condition, in line with the session 2, did not reveal any relationship between the MI and the TI accuracy ($F(1, 18) = 0.397$, $adj.R^2 = 0$, Pseudo $R^2 = 0$, $p = 0.536$, Theil-sen $p = 0.324$) (**Figure 11d**). A summary of the results is presented Table 1.

4 - Summary of the main findings

The present section aims to present a brief summary of the behavioural and electrophysiological findings from this study (**see Table 1**). Negative findings, non-significant p-values or marginal effect size are represented in red. TS.p represents the p-value calculated on the basis of Theil-sen estimator. Ps.R is the pseudo R^2 calculated with the Theil-sen approach. Negative findings, non-significant p-values or marginal effect size are represented in red. TS.p represents the p-value calculated on the basis of Theil-sen estimator. Ps.R is the pseudo R^2 calculated with the Theil-sen approach. Finally, ctrl and tmr respectively stand for the control and TMR condition.

Table 1 | Summary of the behavioural and EEG findings

	Statistical results	
Test procedure	P-value	Effect size
Behavioural findings		
Control vs. TMR S2	$p = 4.17e^{-05}$	Hedge's g = 1.68
Control vs. TMR S3	p = 0.072	Hedge's g = 0.64
Evolution rate control S2.S3	-	+0.02%
Evolution rate TMR S2.S3	-	-13%
Electrophysiological findings (Modulation index)		
Control vs. TMR δ/ɣ	p = 0.044	Hedge's g = 0.63
Control vs. TMR δ/ σ	p = 0.235	Hedge's g = 0.26
Electrophysiological correlates of transitive inference accuracy		
Accuracy ~ MI δ/ɣ (ctrl S2)	p = 0.232, TS.p = 0.810	adj.R^2 = 0.02, Ps.R^2 = 0
Accuracy ~ MI δ/ɣ (tmr S2)	p = 0.901, TS.p = 0.143	adj.R^2 = 0, Ps.R^2 = 0
Accuracy ~ MI δ/ɣ (ctrl S3)	p = 0.069, TS.p = 0.05	adj.R^2 = 0.12, Ps.R^2 = 0.1
Accuracy ~ MI δ/ɣ (tmr S3)	p = 0.536, TS.p = 0.324	adj.R^2 = 0, Ps.R^2 = 0
Accuracy ~ MI δ/ σ (ctrl S2)	p = 0.124, TS.p = 0.001	adj.R^2 = 0.1, Ps.R^2 = 0.1
Accuracy ~ MI δ/ σ (tmr S2)	p = 0.593, TS.p = 0.211	adj.R^2 = 0, Ps.R^2 = 0
Accuracy ~ MI δ/ σ (ctrl S3)	p = 0.269, TS.p = 0.0004	adj.R^2 = 0.02, Ps.R^2 = 0.1
Accuracy ~ MI δ/ σ (tmr S3)	p = 0.741, TS.p = 0.421	adj.R^2 = 0, Ps.R^2 = 0

5 - Discussion

Decades of research brought compelling evidence about sleep-related benefits upon memory consolidation (Diekelmann and Born, 2010b; Dudai, 2012; Rasch and Born, 2013; Denis et al., 2021; Zhang et al., 2022) and at greater extent upon relational memory represented by transitive inference (TI) (Ellenbogen et al., 2007; Golkashani et al., 2021). Building upon replay, considered as a core process of memory integration (Wilson and McNaughton, 1994; Maquet et al., 2000; Peigneux et al., 2004), TMR experiments that aimed to replicate that spontaneous phenomenon observed during sleep rapidly revealed a proven efficiency in the improvement of memory consolidation (Fuentemilla et al., 2013; Sterpenich et al., 2014; Cairney et al., 2018; Goldi et al., 2019), as well as in transitive inference abilities (Santamaria and al., 2023). However, the precise mechanisms involved as well as the condition required to promote TMR-related benefits upon TI are misunderstood. For that purpose, the present study aimed to further knowledge about TMR benefits by focusing on SWS stage and more specifically, on delta and gamma activity as well as sigma activity in humans, two frequency couplings known to play a crucial role in memory integratino (Jensen and al., 2007; Shimizu and al., 2018; Göldi and al., 2019).

Concretely, participants have been trained on series of pairs of items for which half of them were cued via a song. During SWS, cueing song have been re-presented preferentially at the up-phase or the peak of slow oscillations. A subsequent testing session was performed immediately after sleep and after a week to test both short term and long-term evolutions of transitive inference. In this study, the modulation index from delta phase and spindle amplitude but also low gamma one was used to predict TI accuracy.

At the behavioural level, short term as well as long term TI accuracy from the control condition did not reach a significantly higher level than chance. Comparatively, TMR boosting effect resulting in a high accuracy that slightly decrease after a week. The trend from the control condition is surprising as sleep itself has been shown to promote relational memory (Ellenbogen et al., 2007; Werchan and Gómez, 2013; Behrens et al., 2018; Aly et al., 2022) as well as issue-solving skills (Sanders et al., 2019). As raised in the general introduction, degree of awareness is known to positively modulate TI abilities. However, after more careful considerations, it appeared that around 50% of the participants partially or completely guessed the overall objective behind the protocol. Deeper comparison analysis did not reveal a significant difference between participants aware about the hierarchy at the end of the experiment and those who ignored the relationship between items at short term (54.4 versus 54.5% of accuracy) as well as at long term (52.7 versus 58% of accuracy). excepted a small increase of accuracy between sessions for the group aware about the hierarchy. A more convincing explanation might come from the polysomnographic data revealing that among the average of 11 participants that performed at chance level at session 2 and 3, 83% of these were shown to exhibit a small percentage of SWS but also of REM sleep compared to the average usually described in the literature, that has been replaced by N2 percentage. This last argument can be source of interest. Indeed, whether a full night of restorative sleep is crucial for memory integration is not surprising. However, these conclusions bring an insightful information about the mutual role of SWS and REM sleep together as essential to promote memory integration.

At the EEG level, TMR application was shown to promote a strong activity in the sigma range at the stimulus onset, followed by low-gamma frequencies from stimulus onset to 2000 Ms after stimulus. Moreover, a massive peak of delta frequency around 200 Ms before to 500 Ms after stimulus was shown. Finally, this activity was associated with a large band of sigma and low-gamma activity. Though the lack of physiological analysis would make the interpretation challenging, such a dynamic is in line with the assumption about delta frequencies suggested to drive spindle and thus, promote memory consolidation (Fogel and Smith, 2006; Wilhelm and al., 2014). Finally, and as expected, significant clusters in the range of delta, sigma and gamma activity emerged from the comparison between TMR and control conditions. Moreover, a deeper EEG analysis of cross frequency between delta/gamma and delta/sigma activities revealed a significant effect of TMR on the strength of coupling for the delta and low gamma range (around 35 Hz), but surprisingly, not for the delta/sigma activity. However, a much higher strength of coupling between this last coupling was observed.

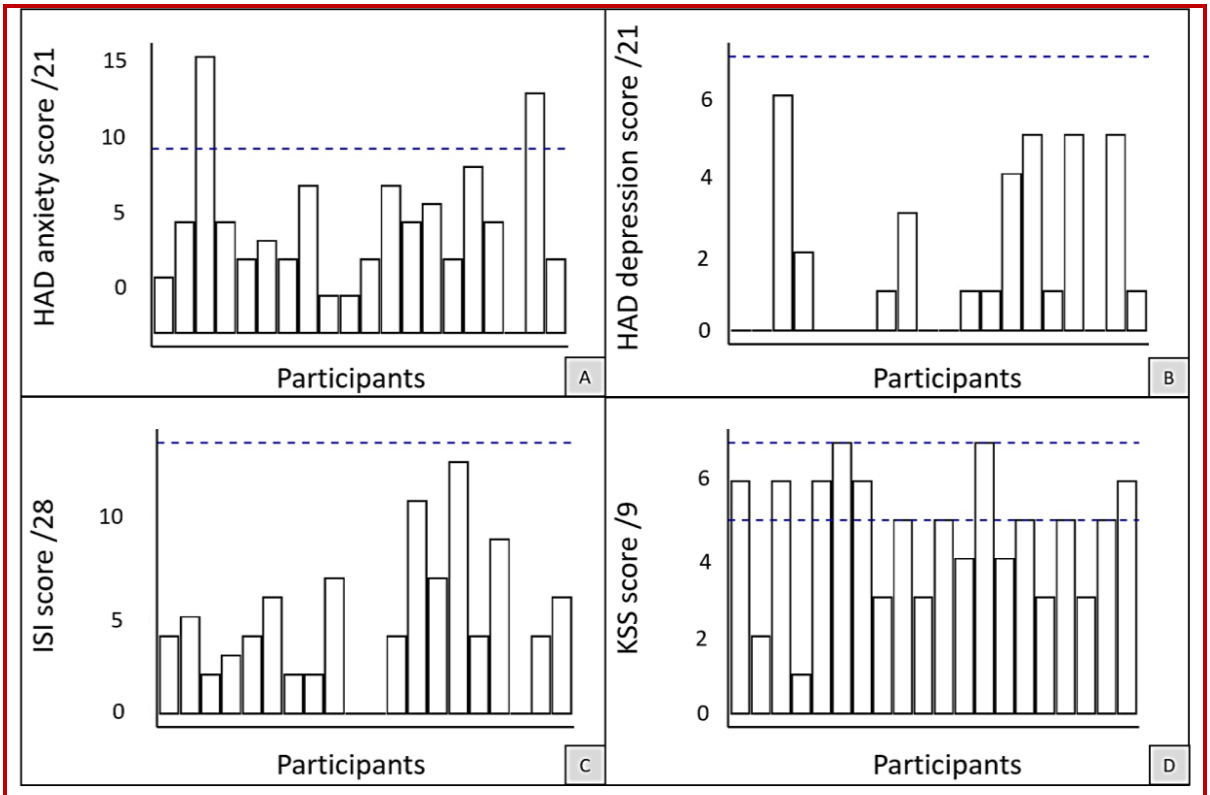
However, and contrary to the main hypothesis, TMR benefits shown at the behavioural level did not appear to predict the correlation between the MI and TI accuracy. Indeed, while positive and significant correlations were found between both couplings and accuracy for the control condition, at short and long-term, TMR condition exhibited at best, flat trends or at worse, negative correlations. A reason proposed to explain the deterioration observed for TMR might come from the phase-locking between SOs and sigma or gamma frequencies. Indeed, while convincing findings in the literature posit the idea of a positive coupling at SO up-phase, the phase-preference analysis in this study revealed a gamma frequency range scattered around the delta phase as well as for both conditions (see Supplementary - S4 and S5). Comparatively for the delta/sigma coupling, and surprisingly, the phase-preference for the control condition appeared phase-locked to the down-phase of SO and thus, positively correlated with TI accuracy, while TMR condition revealed a coupling phase-locked to the up-phase of SOs, associated with a negative or flat correlation with performance. Studies are needed to further knowledge about the phase-locking influence upon memory integration or cognitive flexibility.

All sciences worthy of the name also suffer from limitations and the present study is certainly no exception to the rule. A first source of limitation, common in the field of sleep research, can be raised about the lack of statistical power due to the small sample size. Indeed, a study that aims to detect a medium effect size would expect at least 32 participants (around 26 for repeated measure designs). Here, time limitations led to a small sample size (N = 20), resulting in a loss of probability to detect positive effects when they are real. A second source of limitation is the unique type of item chosen. Here, the choice of imaginary object was motivated by the decision to limit potential bias. Indeed, memory of pictures of scenes can be more important for participants that are used to travel. Moreover, pictures of faces, not to mention prosopagnosia, is associated to very specific cognitive treatments and neural networks for which the efficiency may vary between people. However, it is reasonable to consider that the type of material chosen may have affected transitive inference abilities, and at bigger scale, the memory processing, integration and thus, the EEG dynamics. Finally, future research should consider the idea that classic EEG correlates of performance may not be robust enough to capture sleep benefits. In a field of research where the potential benefits of sleep upon memory integration and cognitive flexibility are still an open question, it is reasonable to think about innovative approach more susceptible to capture those benefits. As an example, recent findings have shown the close relationship between fractals and circadian rhythms (Pittman-Polletta et al., 2013) or more specifically, the importance of fractal approach to predict issue solving (Diaz et al., 2015). Future research should consider the analysis of temporal variations of EEG dynamics as an inspiring source of investigations.

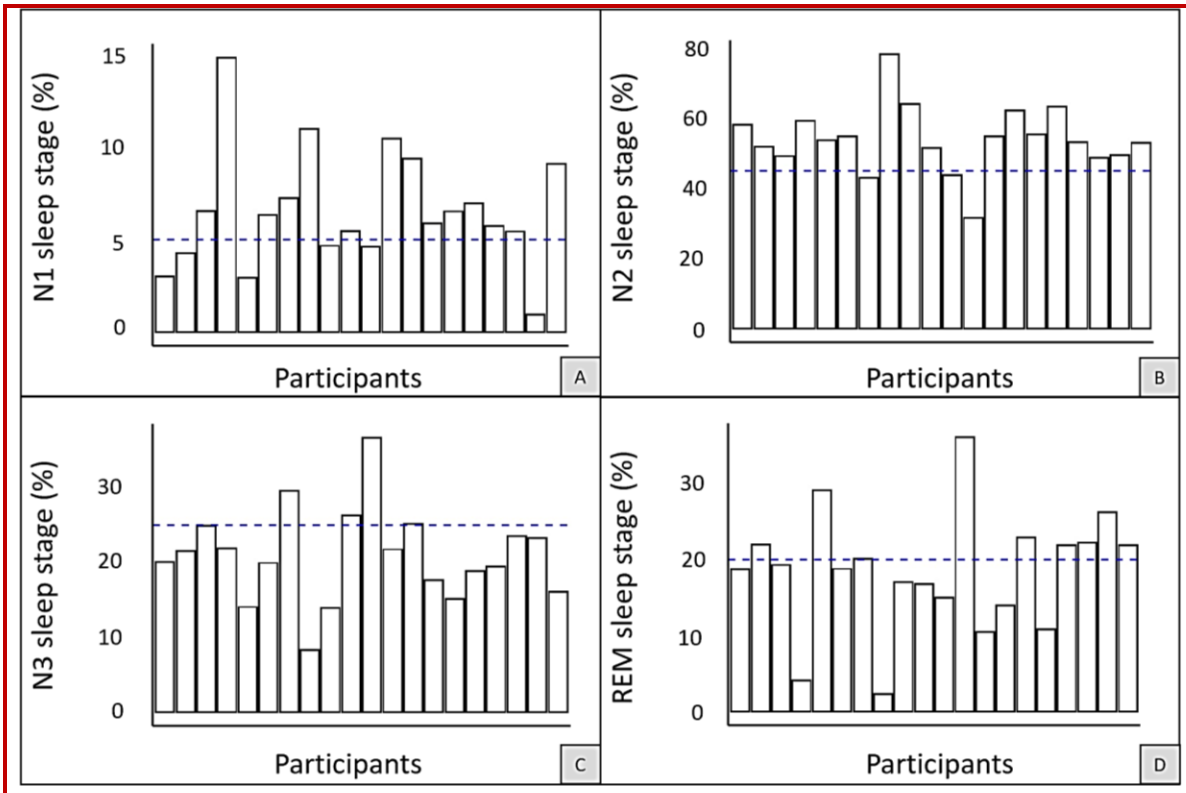
In summary, and despite of these limitations, the present study provided insightful information by the findings about TMR benefits upon transitive inference as well as by the failures to capture convincing neural correlates of TMR-related benefits. By providing evidence about TMR benefits but also the physiological dynamics behind these benefits, and the conditions needed to optimize them, namely a mutual interaction between SWS and REM sleep as well as a careful consideration of the phase-preference between delta and gamma frequencies but also of the stimulation

phase-locking, this study shines a light upon the fantastic interaction between sleep and memory.

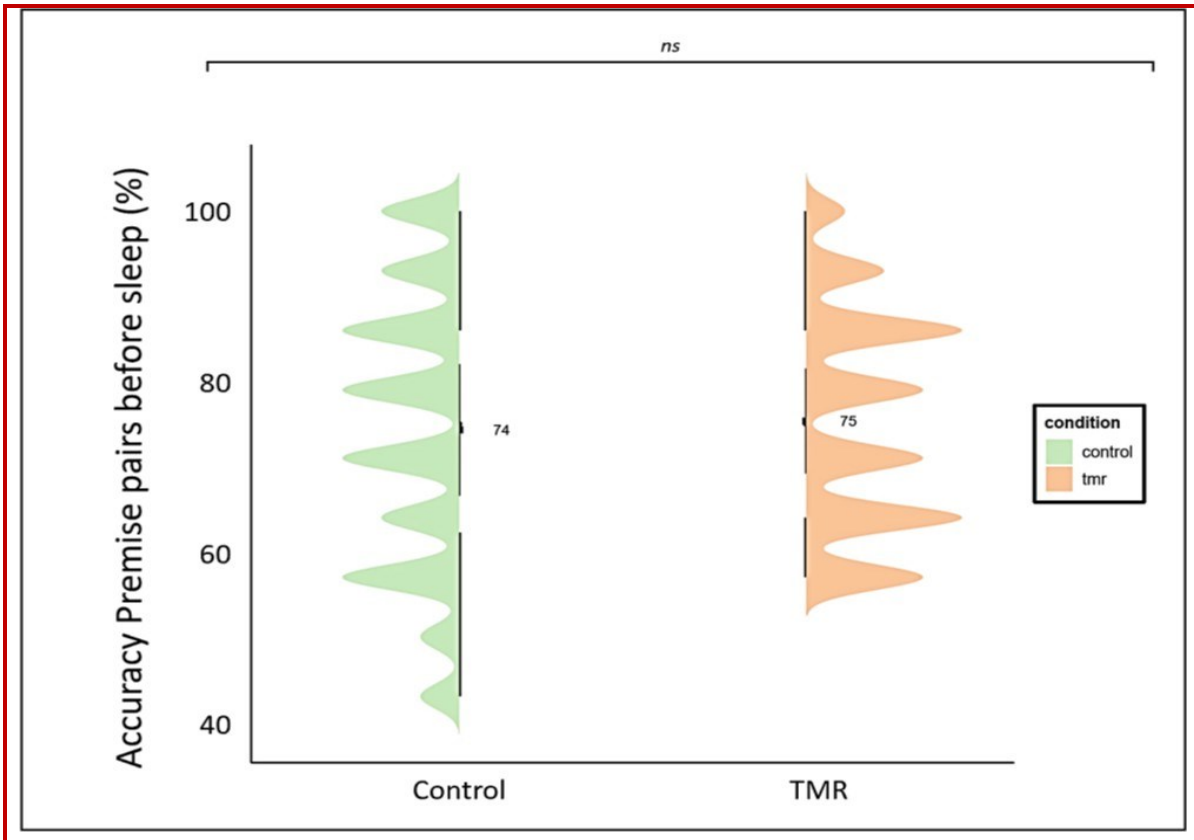
6- Supplements



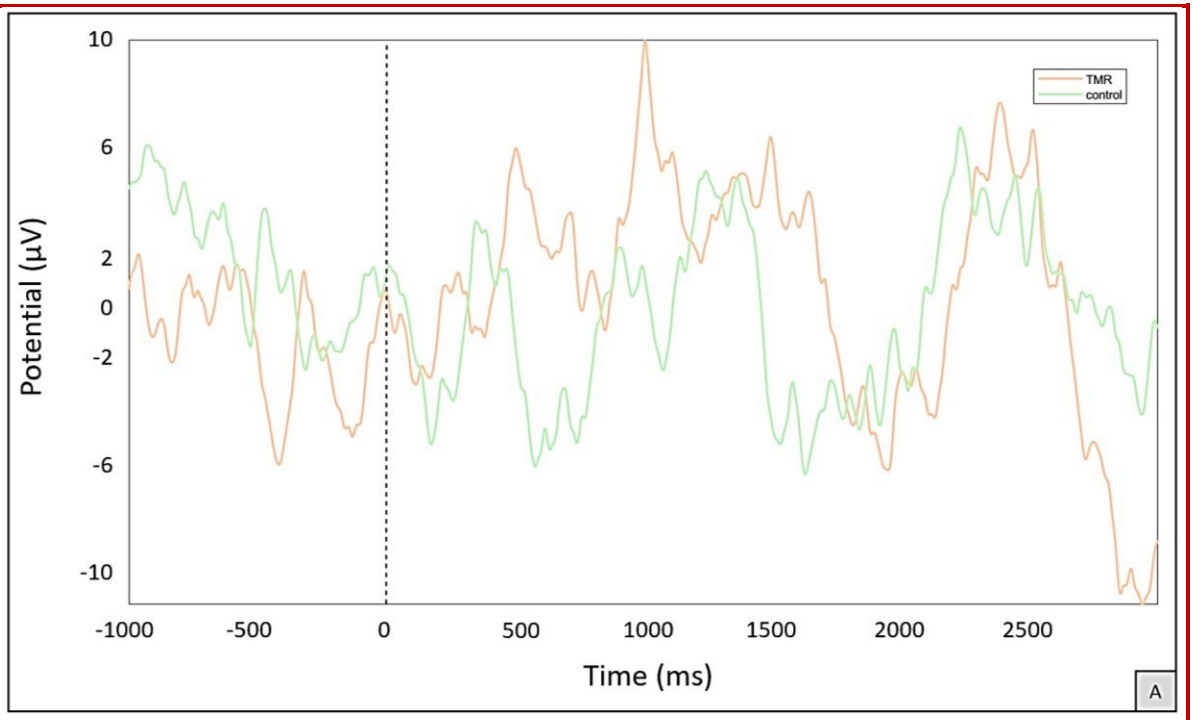
S1: Anamnestic scores per participants. **(a)** 2 participants appeared to reach an anxiety score o 10 or above. However, as their score of depression remained in the area of acceptance, they were not excluded from the study. The dashed blue line represents the threshold of acceptance.



S2: Percentage of time spent by sleep stage per participants. The dashed blue line represents the theoretical time spent considered as normal for a healthy adult.



S3: Graphical representation of premise pairs accuracy before sleep. ns = non- significant



S4: Averaged ERP from all the participant and all channels representing the TMR phase application on SOs. Both conditions appeared phase-locked with the peak of SOs.

Chapter 5: GENERAL DISCUSSION

1 - Thesis overview

The overall objective of the present thesis was to further knowledge about short and long-term application of TMR during SWS or REM sleep and the formation of transitive inference, a form of cognitive flexibility applied in daily life situations. The second objective was to explore the multiple components of electrophysiological brain activity during sleep to detect potential neural correlates susceptible to provide for convincing explanations of TMR behavioural benefits. The reasons behind this project came from a double conclusion from the fact that while numerous findings from animals or humans studies, in the field of cognition or biology, provided for insightful reasons to believe that sleep plays a crucial role in the consolidation of memory, or even in the integration of recent and old memories, the exact mechanisms involved in the formation of memories consolidated sometimes for a lifetime, the evolution of these mechanisms over time and finally, the potential interaction between sleep stages' contribution remained open questions.

On that basis, a series of experiments were designed to assess the sleep promoting effect in the emergence of TI, the role of TMR upon each main sleep stages, namely SWS and REM sleep in TI abilities over time, and finally the electrophysiological neural correlates represented by the strength of coupling between frequencies that could explain sleep and TMR benefits.

The chapter 2 aimed to investigate the behavioural benefits from a full night of sleep compared to a similar period of wake without sleep deprivation, in the consolidation of memory and TI emergence. For that purpose, a TI task was designed where premise components were used to assess memory consolidation and TI elements were used to assess cognitive flexibility. Both cognitive components were examined at short (12 hours after learning) and long-term (a week after sleep). The chapter 3 that was built upon a remote TI task and a home-based TMR device mainly aimed to investigate the role of TMR during REM sleep in the formation of TI and its evolution at short and long-term. The second objective consisted in exploring the exploration of EEG

correlates of TI formation, mainly represented by theta/gamma coupling. At lesser extent, the present study also aimed to further knowledge about the applicability and feasibility of lab-experimental designs at home. The chapter 4 constituted the final experiment of the thesis and aimed to investigate TMR application during SWS and its impact upon TI ability at short and long-term. EEG correlates, namely delta/sigma and delta/gamma coupling strength were also investigated as potential sources of explanations of TMR behavioural benefits. The final chapter of the present thesis aimed not only to point out the contribution of the present findings but also to address the remaining open questions and suggest further investigations susceptible to improve knowledge about sleep's contribution in the formation of cognitive flexibility.

2 - Sleep and memory consolidation

Although the transitive inference protocols from the present thesis mostly focused on relational memory, the first experiment also aimed to test post-sleep premise pairs recall to assess consolidation benefits from sleep. The widely accepted idea whereby sleep plays a crucial role in the formation of memory (Diekelmann and Born, 2010b; Dudai, 2012; Rasch and Born, 2013) has been supported by recent studies (Denis et al., 2021; Zhang et al., 2022). Unsurprisingly, these two studies that used a word-pair task revealed a post-sleep benefit 12 hours after learning. However, and interestingly, sleep benefits sharply decreased (Denis et al., 2021) or event disappeared (Zhang et al., 2022) after 24 hours. Finally, a recent study that used the same paradigm, namely a transitive inference task (Foldes et al., 2023), aimed to replicate the findings from Ellenbogen's team (Ellenbogen et al., 2007) about a strong time and sleep benefits in memory formation. However, testing after sleep did not reveal any difference between sleep and wake group premise pairs' performance. Moreover, the control group appeared to slightly perform better than sleep one. As raised later by Cordi and Rasch findings (Cordi and Rasch 2021), time and sleep benefits upon memory formation might depend on specificities and conditions that are still unclear. While long-term sleep benefits remain unclear, the chapter 2 aimed to shed light upon this open-question. Overall, despite a slight decrease, sleep group performance did not

significantly differ compared to the learning accuracy, compared to the wake group. Moreover, the same trend was observed after a week with a steep fall from the control group, close to chance, while sleep group still managed to perform above chance. Here, a protective effect of sleep against memory decline was observed even after a week. A reason that can be raised to explain this may come from the forgetting curve from Ebbinghaus (Ebbinghaus, 1885) that revealed how the strength of encoding could influence the forgetting curve over time. Concretely, a stronger initial encoding would be associated with a less pronounced memory decline. In the case of the chapter 2, the threshold was set to 80% of encoding, which strongly differs from the 66% from Foldes' team (Foldes et al., 2023) or the 75% from Ellenbogen's one (Ellenbogen et al., 2007). Moreover, in the chapter 4, a higher strength of encoding before sleep was shown to significantly increase the proportion of SWS and decrease REM sleep one. Taken together, a reduced forgetting curve completed by a higher proportion of SWS, a sleep stage assumed to play a crucial role in the consolidation of memory are reasonable arguments susceptible to explain the long-term protective effect of sleep observed. More studies are needed to further knowledge about long-term sleep benefits upon memory consolidation.

3 - Sleep and relational memory

The overall objective of this thesis aimed to further knowledge about sleep's role in relational memory. In the specific case of transitive inference, gist abstraction between encoded events would promote the extraction of rules and the detection of irregularities. However, sleep importance in the formation of associations between events led to mixed results. Indeed, the famous study from Ellenbogen's team tested 56 participants on a transitive inference task following sleep or wake, after 20 min, 12 hours or 24 hours (Ellenbogen et al., 2007). Interestingly, only the delayed testing after 12 or 24 hours led to a high degree of inference ability, with a boosting sleep effect for inference pairs with highest distance degrees. Similarly, transitive inference was found to be improved by sleep and reinforcement (Werchan and Gomez, 2013). Comparatively, sleep compared to a similar period of incubation did not show

significant benefits into a riddle, visual change detection and anagrams the task (Brodt et al., 2018). No more benefits were shown into a magic tricks and insight problems task (Schönauer et al., 2018). Finally, sleep did not appear to promote murder-case solving in a video-game, irrespective of the numerous criteria assessed, namely the reasonableness, consistency, story recall, fluency, flexibility, originality and elaboration skills (Hołda et al., 2020). In the field of transitive inference, Foldes and al. results did not reveal sleep benefits upon inference accuracy (Foldes et al., 2023). Comparatively, the results from the chapter 2 revealed a strong sleep positive effect at short as well as long-term (after a week). The benefits found on the comparison between sleep and wake were confirmed by a logistic regression with an accuracy at 81% (AUC = 0.91; OR = 1.32). For now, providing a convincing explanation to explain that discrepancy is challenging due to the poor number of studies. These findings are all the more surprising in the light of the accuracy found in the chapter 3 and 4 for the control group that did not receive TMR and that exhibited a transitive inference accuracy below or close to chance. Although preliminary explanations were provided about the methodological pitfall assumed to disrupt overlapping representations of premise pairs in the chapter 3 and the lack of SWS and REM sleep in the chapter 4, again, the poor number of studies in this field makes any possibility of explanation highly speculative, excepted potential personal factors such as the feeling of complexity of the task susceptible to promote sleep benefits (Sio et al., 2013).

4 - About TMR and transitive inference

Over last decades, Targeted Memory Reactivation (TMR) appeared as a promising approach to evaluate sleep's role in the formation of memory. TMR is derived from the key concept of reactivation during sleep. Concretely, it has been shown that hippocampal neuron networks involved during encoding of events are spontaneously reactivated during sleep in rodents (Wilson and McNaughton, 1994) as well as in humans (Peigneux et al., 2004), leading to a strengthening of these events (Deuker et al., 2013). A typical TMR protocol, an event is associated with a cue that can be olfactory (Rasch et al., 2007) or more often auditory (Rudoy et al., 2009), during

wakefulness. Following this, the sleeping brain is exposed to the cue, leading to a spontaneous reactivation of the neurons engaged during encoding.

Whether applying TMR during sleep could lead to an additional gain in the ability to extract generalities and promote issue solving has been poorly investigated. In a study where participants were tested in their ability to solve challenge in a video game (Beijamini et al., 2021), sleep versus wake condition comparison revealed a strong and significant increase of proportion of successful participants (from 24% to 62%). However, TMR application during SWS or REM sleep did not result in an additional gain of issue solvers. In the field of transitive inference, findings from Santamaria's team revealed an additional gain of accuracy after TMR during SWS up-phase compared to a similar period of sleep without stimulation (Santamaria et al., 2023) but that did not reach significance. A follow-up session two weeks after revealed a similar trend. Hence, the overall objective from the chapter 3 and 4 was to address the challenging question of TMR application during SWS or REM sleep as a tool that could promote association between premises in order to promote the emergence of abstract rule and guessing of the hierarchy within the premise pairs learnt before sleep.

In the chapter 3, TMR cueing sounds were applied during REM sleep on participants that used a remote headset device at home. After sleep, participants were tested on inference pairs derived from premise items that received TMR or not. Overall, behavioural findings led to a significant and positive TMR effect. At short term level, TMR application led to accuracy significantly higher than chance and a greater accuracy than control condition for which accuracy did not even reach chance. Comparison at follow-up session resulted in a similar trend as observed after sleep for the control group. However, and surprisingly, TMR condition revealed a greater and significant delayed boost of accuracy (+22.4%). In line with these findings, a recent paper for which a similar delayed boosting effect occurred after TMR during REM sleep (Perreira et al., 2023) proposed a delayed phenomenon of plasticity that might take days to occur, and for which behavioural consequences would not be immediately visible. Although the present thesis did not provide any biological results susceptible

to support this theory, numerous recent findings have raised the importance of melanin-concentrating hormone (MCH) neurons that are highly activated during REM sleep (Verret and al. 2003), as a good candidate susceptible to explain the crucial role of REM sleep in neural plasticity. Indeed, a study in mice have found that altering MCH neurons led to a diminution of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-d-aspartate (NMDA) receptor-mediated transmissions involved in the phenomenon of long-term plasticity (LTP). These findings were confirmed by a recent study in which in vitro optogenetic increase of MCH axon activity facilitated hippocampal plasticity by lowering the threshold for synaptic potentiation (Harris and Burdakov, 2023).

In the chapter 4, TMR was applied in the sleep lab and during SWS. As for the chapter 3, the participants were tested at short term after sleep (12 hours after learning) and a week later on their ability to guess inference pairs relationship. At the behavioural level, TMR condition revealed a strong and positive improvement in participants' accuracy both at short and long-term. As for the chapter 3, accuracy from the control condition did not reach a significant difference compared to chance (respectively 54% and 55% at session 2 and 3). Interestingly, TMR benefits appeared to follow a different dynamic with an accuracy from TMR condition that immediately reached a peak at 74% of correct response after sleep. Subsequent testing at follow-up led to a decrease of performance (evolution rate averaged at -13%). These findings are in line with the ASC model (Diekelmann and Born 2010; Born and Wilhelm, 2012; Rasch and Born, 2013) under which slow oscillations during SWS play a key role as main synchronizer. Indeed, depolarizing up-phase of SO are assumed to drive thalamocortical spindles which in return drive the sharp-wave ripples in the hippocampus, promoting memory reactivation and consolidation. While the question of neural correlates and phase amplitude will be discussed in the next section, the averaged ERP across participants and channels in the chapter 4 revealed a TMR application close to the peak of SOs. In line with the results from Santamaria's team for which TMR application during SO up-phase was shown to promote TI compared to down-phase (Santamaria et al., 2023), it is reasonable to assume that TMR during up-phase of SO would increase the phase

coupling between SO, spindles and ripples and thus, promote hippocampal-neocortical memory transfer and consolidation.

However, no convincing explanations can be given about the reason why TMR benefits timing differed between SWS and REM sleep. It is important to keep in mind that in the TMR scope of research, findings about potential benefits are still controversary (Simon et al., 2018; Joensen et al., 2022), SWS and REM sleep's roles implication in memory formation are still unclear (Yuksel et al., 2023) as well as phase-locking preference (Batterink et al., 2016; Santamaria et al., 2023). More studies are needed to address these open questions.

5 - About neural correlates of TMR

The present thesis did not only aim to investigate about TMR benefits but also about potential neural correlates susceptible to explain these benefits. As mentioned in the previous section, while TMR has been mostly shown to promote memory consolidation by increasing recall accuracy after sleep, the reasons behind these benefits are still unclear. For that purpose, questions about TMR have been addressed in the chapter 3 during REM sleep and in the chapter 4 during SWS. Concretely, the chapter 3 aimed to further knowledge about theta and gamma contribution to memory integration and whether the coupling between these frequencies could be improved by TMR. The decision was motivated by the state of the art whereby REM sleep theta oscillations that mostly take their origins from hippocampal activity (Mukai and Yamanaka, 2023) are known to drive slow and fast gamma oscillations (Sirota et al., 2008) that are generated in the subiculum (Jackson et al., 2011). In a study performed in mice (Brankack et al., 2012), theta gamma coupling was found to increase during tonic REM sleep that represents approximately 95% of REM sleep time spent. In human, theta gamma coupling was shown to play a crucial role in memory formation (Canolty et al., 2006; Staudigl, 2013; Heusser et al., 2016) and long-term potentiation (LTP) in hippocampus (Pavlides et al., 1988). The chapter 4 mostly aimed to focus on delta gamma coupling as a potential marker of memory formation. Although investigating

gamma oscillation in SWS was unusual, gamma frequencies were not only shown to be coupled with SO (Steriade et al., 1996; Grenier et al., 2001), mostly during the up-phase of SOs but also to modulates synaptic plasticity (Wespatat et al., 2004). Finally, in human, gamma-frequency activity during encoding was shown to predict recognition and long-term memory (Sederberg et al., 2003; Gruber et al., 2004; Osipova et al., 2006). As a second objective, in line with the ASC model mentioned in the previous section, the coupling between delta and spindle activity has also been investigated as a potential neural correlate of transitive inference.

Overall, physiological findings from chapter 3 started by revealing the presence of theta and gamma approximately 500 ms following stimulus onset. As expected, TMR condition was associated with an increase of these frequencies of interest, as shown by the event-related desynchronization/synchronization (ERD/ERS), a measure of power decrease/increase of electroencephalogram (EEG). In line with the expectations, further analyses revealed an increase of the strength of coupling between theta and gamma frequencies for the TMR condition, measured by the phase amplitude coupling (PAC) modulation index (MI) coefficient. However, the behavioural findings went against the hypothesis about a positive relationship between the MI and TI accuracy. On the one hand, such a positive trend only occurred at follow-up session. On the other hand, and more surprising, it only happened for the control condition. In line with the behavioural findings about the chapter 3 mentioned earlier, a delayed correlations between neural representations of coupling and accuracy are not matter of surprise, although the reason of that delay still remains an open-question. However, the potential detrimental effect of TMR upon the relationship between MI and TI accuracy went completely against the preliminary assumptions. A deeper analysis about phase-preference between theta and gamma revealed a shift in the phase-locking between gamma that appeared down-phase locked with theta in the TMR condition, while gamma was shown to be up-phase locked with theta frequency for the control condition. Interestingly, theta low-gamma coupling is mostly known to be up-phased with theta band (Schomburg et al., 2014; Lopes Dos Santos et al., 2018; Zhang et al., 2018). Hence, it is reasonable to assume that the reason why only the endogenous theta gamma coupling from the control condition appeared to be

positively associated with behavioural performance would be due to the preferred phase-locking between frequencies, compared to the TMR condition that potentially altered the theta gamma phase-locking. Finally, a temporal cluster analysis raised the significant progressive decrease of phase amplitude coupling that progressively derived from low-gamma to beta band for TMR condition. While it might be challenging to determine whether phase shifting or coupling amplitude decrease went first, it is plausible to suggest that they both influenced the detrimental TMR effect found between MI and TI accuracy.

Findings from the chapter 4 revealed the presence of delta 200 ms before stimulus onset and sigma frequency range locked with the cueing sound. This interesting physiological dynamic is in line with the ASC model and the SOs assume to drive the spindles. Moreover, low gamma clusters appeared spread around the stimulus onset. However, only spindles from the control frequency were shown to exhibit a higher ERDS value compared to TMR. While the reasons of such a discrepancy between the time frequency clusters found in delta, spindles and low gamma range and the lack of expression of power in the ERDS are unclear, three arguments are proposed here. First, frequency-specific effects or the fact that while delta and low gamma power might show a consistent increase, spindles within the same time windows might not exhibit similar changes, leading to nuanced ERDS outcomes. A second interpretation is related to interactions between frequencies. Indeed, an increase in spindle power might be accompanied by changes in other frequency bands that mask or modulate the ERDS effects specifically for delta and gamma range. Finally, variations in neural responses among individuals could contribute to complex patterns, where group-level differences in power might not necessarily translate directly into ERDS changes due to the variability in how individuals respond within each group. Interestingly, delta spindle coupling was shown to exhibit a much higher and significant MI compared to the delta low gamma coupling. However, only delta low gamma coupling was shown to significantly increase with TMR. The reason why delta spindle coupling did not significantly increase with TMR can be explained by the fact that cueing sound was phase-locked with the peak of SOs, varying from the ASC model for which spindles are locked to the up-phase of delta oscillations. As for the chapter 3, a regression

analysis was performed between the MI from delta spindle and delta gamma coupling and TI accuracy at short and long term. It is important to raise that only robust Theil-Sen regression found significant relationships between couplings and behavioural accuracy. Concretely, a positive and significant relationship was found between MI and spindle frequency at short and long term but only for the control condition. Moreover, a delayed positive relationship was also found for the delta gamma coupling and TI accuracy. Again, the phase preference between the delta phase and the spindle or gamma amplitude can provide insightful explanations about the detrimental TMR effect observed similarly to the chapter 3. Indeed, the results from phase-preference analysis revealed that higher PAC values in the delta gamma coupling was more associated with a down-state phase-locking for the control condition compared to TMR for which the phase-locking tended to be more up-phased. However, it has been shown that endogenous gamma amplitude tends to be down-phased with the delta phase, in rodent (Andino-Pavlovsky et al., 2017) as well as in human (Gagol et al., 2018). On that basis, it is again reasonable to suggest that applying TMR would have induced a shift in the phase-preference leading to detrimental TMR effect upon PAC coupling. In the case of delta spindle coupling, spindles appeared more phase-locked with the up-phase of slow oscillations in the control group, compared to the TMR group. As mentioned before, ASC model posits the idea whereby spindles are driven by slow oscillations at the up-phase. Building on this observation, it is plausible to admit that TMR again modified the phase preference between delta and spindles resulting in variations of coupling and loss of relationship between MI strength and TI accuracy. Although the phase-preference may appear as a convincing argument to explain the alteration between MI and TI accuracy by TMR, this argument suffers from two major limitations. First, one must admit the noisiness of phase-preference analysis presented in the chapter 3 and 4. The reason behind this comes from the fact that the overall objective here was to test TMR benefits upon behavioural transitive inference without taking the phase-locking into consideration during the building of the experiment as a main priority. Retrospectively, it clearly appears that this point should have been more carefully considered. The second limitation comes from the absence of EEG analysis at long-term (at follow-up session). While phase-preference analysis

can provide information about the difference between TMR and control conditions at short term, the reasons of such a similar difference at long term is more challenging.

Taken together, findings from the chapter 3 and 4 provided and convincing and insightful elements about the EEG dynamics associated with the integration of memory in human, raising the importance of gamma coupling with theta oscillations during REM sleep and with spindles during SWS as good neural correlates. Moreover, and importantly, findings highlighted to what extent TMR should be carefully applied, and to what extent careful considerations should be taken about the respect of endogenous phase-preference between frequencies.

6 - Home-based application of TMR

It cannot be excluded that the present thesis has been intensively impacted by the sanitary restrictions due to COVID-19 pandemic. Due to numerous restrictions, the experimental chapter 3 has been designed to be performed remotely. On that basis, numerous questions were addressed, namely the question of validity of the measures and output from the device, the ability to capture EEG dynamics with a small number of channels, the autonomy given to the participants, and the comfort of the device, as potential experimental bias. Surprisingly, the Z-max headset was shown to capture EEG signal and deliver TMR with a high degree of efficiency as confirmed by a recent study (Esfahani et al., 2023). In the last few years, TMR applied in real life conditions was shown to promote memory consolidation but only under certain conditions, namely no sleep disturbance (Goldi et Rasch, 2019) or noisy stimuli (Whitmore et al., 2022). In the case of the present thesis, Zmax headset has provided convincing proof of elements about benefits from potential future applications in real-life. As raised in the chapter 3, in a world where approximately 62% of adults feel they do not get enough sleep, it is reasonable to imagine a future where TMR could potentially enhance sleep habits, optimize the onset of sleep phases, and provide valuable support in managing mood disorders, memory integration or creativity.

7 - Limitations and future directions

The present thesis like any scientific research suffers from important limitations that need to be raised to the reader.

The first limitation that mostly concerns the chapter 3 and 4 is the lack of power. On average, 23 participants per group (N chapter 2 = 21, N chapter 3 = 28, N chapter 4 = 20) were recruited for each experiment. at the behavioural effect, the sample size needed to reach 80% of probability to detect a medium effect when it actually exists (true positive) is around N = 32. In the case of the present thesis, the power is reduced in a way that the probability to detect true positive is around 50% of chance. On the other hand, a small sample size also increases the type II error, namely the probability to reject an effect when it actually exists. The reader should carefully integrate the present limitation when considering the findings in the present thesis. A second source of limited power is the small number of epochs in the chapter 3 that participants had in common (N = 40). Only 40 epochs per condition make subtle effects harder to detect, decrease the signal-to-noise ratio, thus affecting the reliability of the results. Here again, the reader should interpret the findings in accordance with the limitation of the dataset's size. A second source of limitation comes from the lack of control procedures. Among these, the presence of adaptation nights before wire-up in the lab or at home would reduce the potential sleep disturbance and EEG bias, leading to a greater accuracy of the results. In the case of TMR, a sham condition comprising of a sound not semantically related to the material learnt before sleep would provide for insightful elements about how a simple sound can modulate brain signal. Finally, and due to the evolution of behavioural accuracy over time raised in the chapter 3, it would be essential to propose additional testing sessions to improve knowledge about potential delayed sleep benefits.

Beyond the present limitations raised, potential new lines of research are proposed. Building on the physiological differences between tonic and phasic REM sleep stages, it would be interesting to investigate about their respective implications in the

formation of memory, their interactions, and finally, the difference of EEG dynamics behind these stages. Secondly, and while the field of sleep research is mainly dominated by a dichotomic consideration of sleep stages, further investigations about SWS and REM sleep interaction would provide for an important source of knowledge about the overall process of memory integration during sleep. Finally, it would be interesting to open the field of EEG by deploying innovative signal analysis based on the non-stationarity nature of the brain signal. Derived from the fractal theory of chaos (Pritchard et al., 1995; Accardo et al., 1997), multifractal non-stationarity of EEG signal, namely a signal that exhibits a high degree of complexity and irregularity in its structure due to multiple scaling exponent, has been shown in numerous pathological conditions like major depression (Linkerkaer-Hansen et al., 2005; Bachmann et al., 2013), Alzheimer disease (Montez et al., 2009; Zorick et al., 2020), schizophrenia (Nikulin et al., 2012) or epilepsy (Monto et al., 2007; Polychronaki et al., 2010). At the cognitive level, non-stationarity signal features appeared to be a reliable predictor of performance in problem solving tasks (Diaz, 2015) and cognitive flexibility (Lu, 2023). Hence, multifractal approach can provide for a mathematical framework for modelling and understanding complex systems by capturing the multifaceted and dynamic nature of the signal. Indeed, multifractal detrended fluctuation analysis (MFDFA) has proven its ability to systematically eliminate trends of various order caused by external effects and reduce noise caused by imperfect measurement and catch scale-free dynamics of the signal (Chen et al., 2002; Stam, 2004; Jiang, 2005; Linkerkaer-Hansen et al., 2007; Malinowska, 2019; Päeske et al., 2023). Used in numerous fields of research, MFDFA has a proven and very high power of classification of frequency bands (AUC from 0.85 to 0.95) (Finotello and Zanon, 2015) or functional coupling like between delta and gamma band (Fell et al., 2003).

8 - Conclusion

The present thesis overall objective was to further knowledge about short and long-term evolution of relational memory following TMR application during REM sleep or SWS. The investigation of EEG dynamics associated with TMR provided insightful

elements of proof about the crucial role of sleep in the extraction of rules and the associations of events to shape innovative knowledge. The EEG analysis performed at different sleep stages shed light upon the complex EEG dynamics and sleep stage specificity as potential markers of memory integration, namely the delta spindle coupling but more surprising, the delta low-gamma coupling in SWS, and the theta gamma coupling, well documented in animals but poorly investigated in humans. Further analysis also raised the importance of carefully consider the endogenous phase-preferences between coupling and their impact upon the strength of coupling and behavioural benefits. Last but not least, findings confirmed the high potential of TMR application in real-life condition in multiple fields like memory integration as well as mood regulation or sleep monitoring. Taken together, findings from the present thesis, although modest, brought another building block to the edifice. However, many more steps are needed to fully understand the exact mechanisms and reasons about why we spend a third of a life sleeping.

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