Sleep disconnection : EEG decoding of covert attention during different vigilance states

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THÈSE DE DOCTORAT
DE L'UNIVERSITÉ PSL

Préparée à l'École Normale Supérieure

La Déconnection du Sommeil
Décodage EEG de l'Attention Couverte dans Divers États de Vigilance

Soutenue par

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Le 03 07 2020

École doctorale n° 158

Cerveau, Cognition, Comportement

Spécialité

Neurosciences

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SLEEP DISCONNECTION:

EEG DECODING OF COVERT ATTENTION DURING DIVERSE VIGILANCE STATES

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Dissertation for the degree of Doctor in Philosophy

Under the supervision of Sid Kouider

juillet 2020

Laboratoire de Sciences Cognitives et Psycholinguistique

Ecole Normale Supérieure

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"Because I am acting against the coming laws on retirement pensions and Pluriannual Programming of Research (LPPR), I have changed my schedule and reduced my teaching and research activities. Emails dealing with the current action have my priority."

SUMMARY

Sleep is by essence a closed-loop process. Sleepers stop interacting with the external world and are engaged in their own mental activity. Consequently, probing cognitive functions during sleep is challenging since cognitive psychology traditionally relies on the analysis of behavioral responses. In this thesis, we turn the experimental disadvantage of the sleep disconnection to turn it into a force. We know indeed that sleepers remain sensitive to external information, as exemplified when we wake up upon hearing our alarm clock. We make the hypothesis that understanding how the regulation of sensory disconnection is modulated by internal activity during sleep would give us an insight into inner processes occurring during sleep. To do so, we record brain activity with electroencephalography (EEG) to circumvent the limitations of the absence of motor activity during sleep. We will conjointly identify markers of mental activity during sleep and decode the neural responses to complex auditory stimuli. This will allow us to investigate the factors in sleep neurophysiology that either promote (experiment 1) or suppress (experiment 2) the selective processing of external information. Going one step beyond traditional approaches in cognitive psychology, we developed a closed loop paradigm with a brain-computer interface that targets specific features of sleep endogenous processes (experiment 3).

RESUME

Le sommeil est par essence un processus en boucle fermé. En effet, le dormeur n'interagit plus avec l'extérieur et ses actions se traduisent dans son propre monde mental. Déterminer les fonctions cognitives du sommeil représente donc un défi car la psychologie cognitive s'appuie traditionnellement sur l'analyse des réponses comportementales. Dans cette thèse, nous transformons ce désavantage expérimental en une force. Nous savons en effet que les dormeurs restent sensibles aux informations externes, comme cela est démontré quand nous nous réveillons lorsque nous entendons une alarme. Nous faisons l'hypothèse que comprendre comment la déconnexion sensorielle dépend de l'activité interne du sommeil nous donnera un éclairage sur les processus internes du sommeil. Pour ce faire, nous enregistrons l'activité cérébrale au moyen de l'électroencéphalographie (EEG) afin de contourner les limitations dues à l'absence d'activité motrice pendant le sommeil. Nous allons conjointement identifier les marqueurs de l'activité mentale du sommeil et décoder les réponses neurales à des stimulations auditives complexes. Ceci nous permettra d'interroger les paramètres de la neurophysiologie du sommeil qui soit promeuvent (étude 1), ou suppriment (étude 2), le traitement sélectif des informations externes. En allant plus loin que les approches classiques de psychologie cognitive, nous avons développé un paradigme en circuit fermé utilisant une interface cerveau-machine qui cible des aspects spécifiques de l'activité interne du sommeil (étude 3).

ACKNOWLEDGEMENTS

Thank you first and foremost to the members of the Jury, Philippe Peigneux, Hélène Bastuji, Daniel Pressnitzer, Francesca Siclari, Mélanie Strauss and Gabrielle Girardeau. It is an honor to be evaluated by researchers who inspire me and have already contributed decisively to this thesis. This work is indeed a collective effort. I want to express my gratitude particularly to Sid Kouider, my supervisor. His experience and his vision define my scientific inspiration. His confidence gave me the necessary strength to overcome my fears. I want also to thank M. Emmanuel Gardinetti and the DGA section "Hommes et Systèmes" for funding this PhD project. The foundation of my work has been laid down by Thomas Andrillon. He makes research easy and accessible for others and his help is like the cake under the cherry. Damien Léger offered at Hotel Dieu more than a place to run experiments. His kindness and expertise made me feel welcomed and highly privileged to work in such a place. The Center of Sleep and Vigilance at Hotel Dieu is full of wonderful people who have been comprehensive with an inexperienced researcher and provided their precious help throughout all my studies. Maxime Elbaz provided me optimal experimental conditions and discussions with him opened my curiosity to the endless ways by which sleep can be investigated. Emilie Pépin was essential to my work and ensured everything could work perfectly. Stéphane, Laurent, Claire, Brice and every person that I met at Hotel Dieu impressed me in their own way and made this thesis count as an invaluable experience. Mounir Chennaoui from IRBA provided his expert help and has been a reference for me from start to finish and will stay in the future.
My warmest thoughts are for Célia Lacaux who helped me grow as a human and a researcher. Working with Irene Altuna Echeverria felt natural and I wish to keep collaborating with her. Abla Aloui Soce was also very helpful and a sweet person. Jean-Maurice is a friend and I thank him for his help and passionate discussions. Nicolas' knowledge and skills impress and inspire me. Benjamin Rebouillat contributed to my intellectual and personal development more than I can write. Charlotte Van den Driessche is someone that defies categories and allowed me to feel comfortable to write my thesis. All of the LSCP and DEC members shaped my research by their expert help and provided me with an incredible working environment.
All my research heroes (Karim, Ueli), Jakob Hohwy who hosted me and opened me to fundamental ideas, A. Elbakyan who created sci-hub, ALIUS and Martin Fortier who planted seeds in some many minds and hearts, people mobilized against unjust reforms that uglify academia and society. Finally, I thank with all my heart my friends and family, my mother, my father, my sisters who believe in me, and Hélène whose presence makes me flourish.

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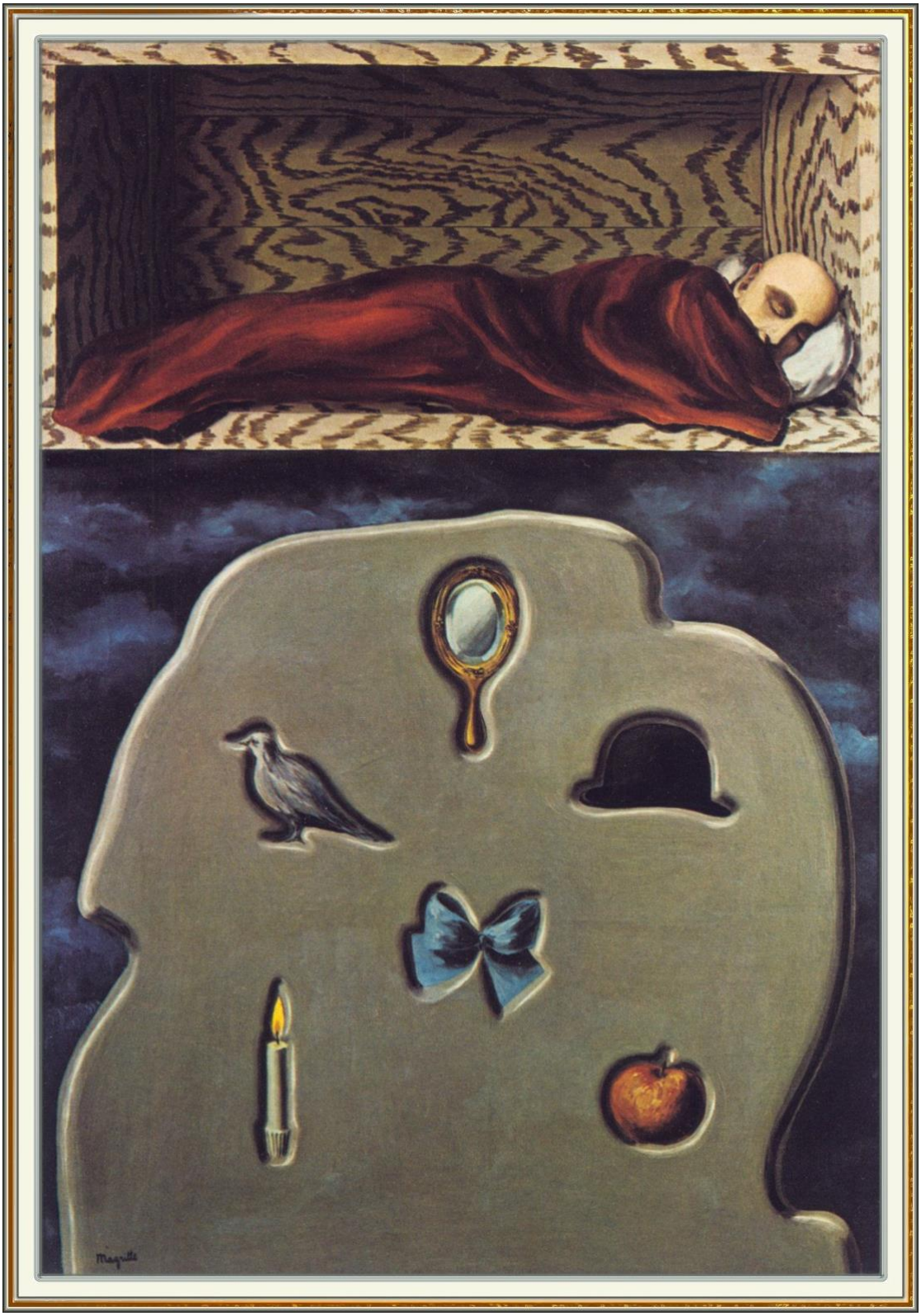
List of Abbreviations and Acronyms

AASM	American Association of Sleep Medicine
BCI	Brain-computer interface
CI	Confidence interval
EEG	Electroencephalography
EM	Eye Movement
EMG	Eectromyography
ENS	Ecole Normale Superieure
EOG	Electrooculography
fMRI	functional Magnetic Resonance Imaging
GH	Growth Hormone
ICA	Independent Component Analysis
MEG	Magnetoencephalography
NREM	Non-Rapid Eye Movement
PPL	Phase-Locked Loop
pREM	phasic REM
REM	Rapid Eye Movement
SD	Standard Deviation
SEM	Standard Error to the Mean
SHY	synaptic homeostatic hypothesis
SWA	Slow-Wave Activity
SWS	Slow-Wave Sleep
tREM	tonic REM

1 GENERAL INTRODUCTION

In this section, we will introduce the scientific context that contributed to starting this thesis. We will thus present the theoretical and experimental works that allowed us to define the main scientific question and formulate testable hypotheses.

"Nothing makes sense in biology if not in the light of evolution" (Dobzhansky, 1973)



Magritte, the reckless sleeper (1928)

1.1 The paradox of sleeper's disconnection from outside world

1.1.1 The limits of introspective approaches of sleep

Sleep makes up 30% of our adult life but yet remains a mystery for the conscious mind. **Mental activity during sleep is indeed covert which means that it is not translated into actions in the external world**. It is only after awakening that inner experiences from sleep can be reported to others. Yet, only glimpses of memories about what happened during sleep usually remains, a phenomenon called dream amnesia (Nir & Tononi, 2010). To explain why memories of dreams tend to vanish at awakening, a first possibility is that memory may be less reliable to retrieve information from sleep after awakening (Nir & Tononi, 2010).

Another possibility is that memory formation during sleep might be impaired. For example, dream content shows alterations in attentional abilities that can lead to a lower efficiency of memory encoding (Sutton et al., 1994; Chun & Turk-Browne, 2007). Finally, the lack of memories at awakening could also be explained by periods of reduced mental activity, notably involving the absence of conscious activity (Tononi & Massimini, 2008). To test these hypotheses, experimental protocols investigating the nature of sleep cognition are needed.

Sleep is a natural, daily, reversible and spontaneous phenomenon that is experienced by every human (if not every animals) (Cirelli & Tononi, 2008). In this respect, sleep is a phenomenon ideally suited for experimental investigation. **Yet, the psychological investigation of its cognitive nature is challenging**. Indeed, cognitive psychology paradigmatically relies on interpreting behavioral data in controlled experimental settings. Yet, in the absence of motor activity by the sleeper, the only way to get behavioral data is to wake up the subject and collect a dream report. Yet, doing so interrupts the very process that is the object of investigation. Additionally, studies investigating the influence of external stimuli presented during sleep on dream reports produced contrasted results (Arkin & Antrobus, 1991, see Table 1 for a summary of findings). Finally, whether dream reports accurately reflect mental activity during sleep has been an ongoing debate which cannot be resolved *a priori* (see Malcolm, 1958 for an early critique and Windt, 2013 for a more nuanced take). To investigate the nature of sleep, one may take a step back from introspective methods and rely on an operational definition that allows its study across animal species.

Table 1 **Summary of findings of incorporation into dream reports of external stimulation presented during sleep.** Direct incorporation refers to the incorporation of the stimulus in the dream as it was presented. Indirect incorporation refers to incorporation of some of the properties of the stimulus or content related to the stimulus but not the stimulus itself. Absence of incorporation refers to failure of incorporating the stimulus or at rates below 10 percent.

Main results	Somatosensory	Auditory	olfactory	Visual
Direct incorporation	Maury in Freud, 1900 Dement & Wolpert, 1958 Koulack, 1969; Nielsen, 1993; Nielsen et al., 1993; Leslie & Ogilvie, 1996	Berger, 1963 ; Hoelscher et al., 1981	De Saint-Denys, 1867; Trotter et al., 1988	LaBerge & Levitan, 1995
Indirect incorporation				Conduit et al., 1997
Absence of incorporation	Cubberly, 1923; Solomonova, 2017	Dement & Wolpert, 1958	Schredl et al., 2009; Okabe et al., 2020	Dement & Wolpert, 1958

1.1.2 The definitions of sleep

Adopting an outsider perspective to characterize sleep, three behavioral criteria have been identified. They were summarized as follows (Peigneux et al., 2001):

- A recognizable posture
- A lack of behavioral responsiveness to external stimulation
- A homeostatic process where sleep deprivation results in a rebound

The first criterium defines sleep as a behavioral state. The second criterium additionally characterizes sleep as a period of disconnection from the external world. Sleep disconnection is here defined as the reduction of response to external stimuli during sleep. It can be assessed by measuring the arousal threshold, i.e. the lowest intensity of sensory stimulation that elicits a physiological response. **Arousal thresholds are typically elevated during sleep compared to quiet wakefulness** (Kohlschütter, 1863). The third criterium defines sleep as a regulated process. Indeed, sleep happens regularly in a reversible way, distinguishing it from other disconnected states such as anesthesia or coma states.

These behavioral criteria have been complemented by neurophysiological criteria. **Brain recordings during sleep in humans have revealed the apparition of a cerebral rhythm**

of large amplitude at a frequency between 0.5 and 2 Hz named slow waves (Loomis et al., 1937; Iber et al., 2007). Measures of arousal thresholds correlate with slow-wave activity (SWA) and sleep restrictions lead to enhanced SWA along with increased sleep duration (Williams et al., 1964). This confirms that SWA correlates with the behavioral criteria of sleep. In addition to slow waves, a diversity of brain patterns has been observed during human sleep (Loomis et al., 1937). Of particular interest is a state that was identified as being associated with dreaming and composed of a desynchronized brain activity and quite similar to wakefulness (Blake & Gerald, 1937; Gottesmann, 2009; Figure 1A).

This stage is characterized by a high arousal threshold and a lack of muscular activity, ensuring the disconnection from the sleeper with the external world. Because this state mixes features of awake activity and behavioral inactivity, it was named paradoxical sleep (Jouvet, 1965). Yet, muscular tonus is not abolished for the oculomotor systems, and eye movements have been noted as a hallmark of this sleep state eponymously named rapid eye movements (REM) sleep (Dement & Kleitman, 1957). By contrast, the rest of sleep is called non-REM (NREM) sleep (Iber et al., 2007). Interestingly, restrictions of REM sleep also lead to an augmentation of REM sleep duration in the subsequent sleep session, a phenomenon called REM rebound (Beersma et al., 1990). The presence of a REM rebound is thus fitting the third criterium of the operational definition of sleep. **It shows that, despite relying putatively on different mechanisms to ensure disconnection and homeostatic regulation, NREM and REM both possess the set of features that define sleep.** To understand what drives commonalities and specificities of sleep, one may take an evolutionary insight into sleep patterns and investigate the factors that drive the selection of these traits.

1.1.3 The evolutionary paradox of sleep

Relying both on behavioral and physiological definitions, sleep has been identified across the whole animal kingdom (Cirelli & Tononi, 2008). As NREM and REM sleep were discovered in several phylogenetically distant species, it was hypothesized that REM sleep and NREM sleep might have appeared multiple times during evolution, a phenomenon called functional convergence (Rattenborg & Martinez-Gonzalez, 2015; Figure 1B). Yet, the evolutionary origins of different forms of sleep remain to be clearly elucidated (Ungurean et al., 2020). Indeed, sleep patterns similar to slow waves and muscular activity akin to muscle twitches found in REM sleep have been identified in zebrafish (Leung et al., 2019). Even in

invertebrates such as flies and cuttlefish mollusks, recent studies point towards the existence of two different sleep states with behavioral similarities with NREM and REM sleep stages (Iglesias et al., 2019; Yap et al., 2017). **The apparition of the same functions across the animal kingdom, or conversely their conservation throughout evolution, are in both cases indicating that sleep is highly adaptative.**

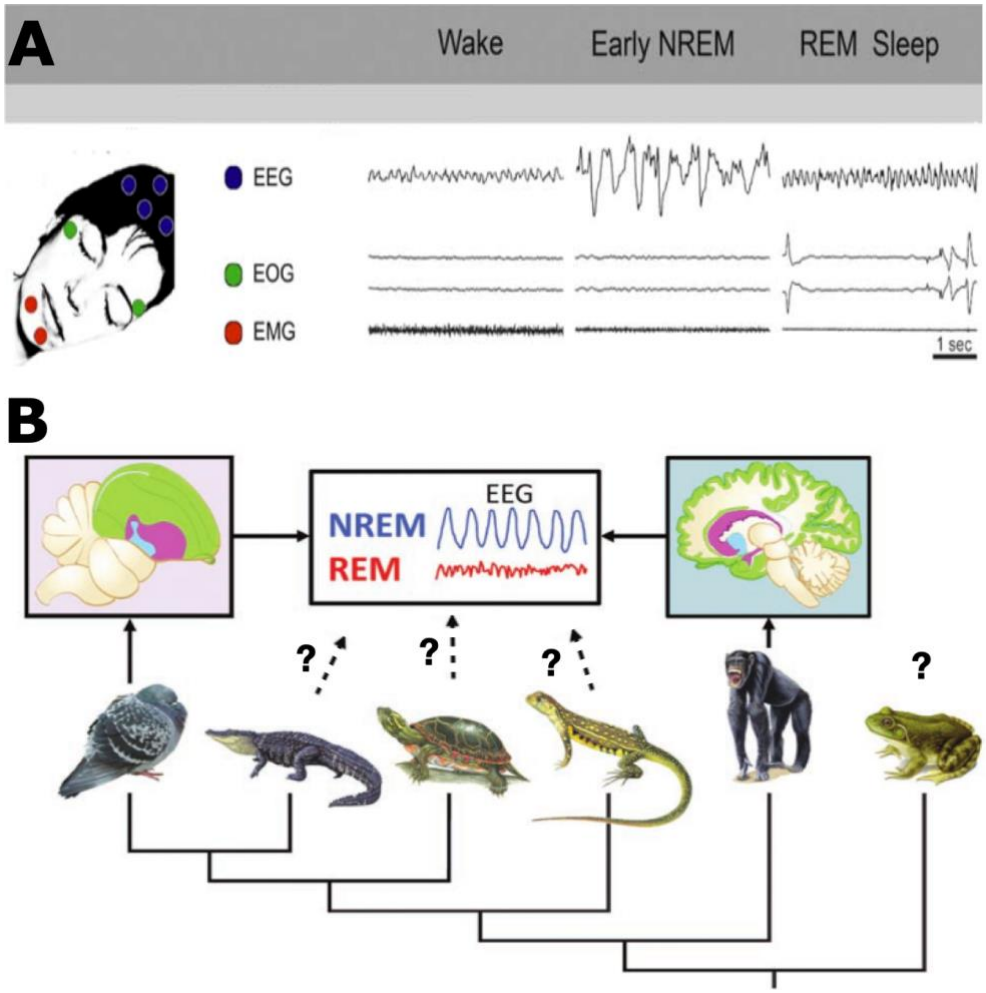


Figure 1 **Diversity and plasticity of sleep states.** (**A**) Division between early NREM sleep and REM sleep as evidenced by electrophysiological measures. Electroencaphalography (EEG) measures the brain responses from the cortex and reveal similar patterns between wakefulness and REM sleep. Conversely, early NREM sleep shows typical slow waves. Electroocculography (EOG) measuring eye movement activity further distinguishes between NREM and REM sleep. Low muscular tonus measured by electromyography (EMG) distinguishes REM sleep from both NREM and awake state. From Nir & Tononi, 2010 (**B**) Both NREM and REM sleep have been found in mammals and birds. While these sleep characteristics are shared by mammals and birds, evidence for these states in other evolutionary classes are mixed or poorly documented. Adapted from Rattenborg et al., 2012

The decreased responsiveness to external stimuli during sleep represents yet *prima facie* an evolutionary cost as it could prevent sleepers from responding to external threats and make them vulnerable. **Thus, sleep disconnection constitutes a paradox: as an evolutionary pressure, it should be counterselected, yet, it is largely conserved across evolution.** While the operational definition of sleep furnishes criteria to define sleep, it crucially lacks to explain why sleep disconnection and sleep homeostasis are associated and why they have been selected together throughout evolution.

In order to solve the evolutionary paradox of sleep, several hypotheses linking sleep disconnection and homeostasis can be formulated:

- sleep disconnection directly serves a homeostatic function that outweighs its cost.
- sleep disconnection is a mere consequence of a homeostatic function that outweighs the cost of disconnection
- sleep disconnection is a necessary condition for the realization of a homeostatic function that outweighs the cost of disconnection

The first hypothesis suggests that mechanisms of disconnection during sleep shape homeostatic functions of sleep. The second hypothesis suggests that disconnection mechanisms would be shaped on the contrary by homeostatic functions of sleep. Finally, the third hypothesis suggests that the mechanisms of sleep disconnection could be unrelated to the mechanisms of the homeostatic function, but the latter would opportunistically benefit from being disconnected from the outside world. In the next section, we will present arguments addressing these three hypotheses. These three hypotheses are not mutually exclusive but map out the possibilities describing how essential features of sleep could be evolutionary co-selected. **To solve the evolutionary paradox of sleep disconnection, we will thus explore in what measure sleep disconnection is related to sleep functions**. To do so, we will restrict this study to the case of mammals.

1.2 The function of sleep disconnection

1.2.1 Disconnection as conservation

Sleep may render prey more vulnerable to their predators. Yet, it has also been suggested that immobility could actually make the sleeper less detectable than during wakefulness. Behavioral inactivity during sleep can be compared to tonic immobility, a widespread form of adaptive behavior that feigns death in the face of danger (Overeem et al., 2002). Shared mechanisms have even been proposed for tonic immobility and REM sleep, which are both characterized by muscular atonia (Tsoukalas, 2012). Thus, **immobility may help to escape predation** (Meddis, 1975). Overall, this hypothesis explains why sleep might be linked to behavioral inactivity but does not explain why sleep would be homeostatically regulated.

Sleep has been compared to hibernation, a period of disengagement towards the external environment to save energy (Figure 2). This parallel is buttressed by the similarity of the physiological phenomena happening in both states such as reduction of temperature, elevated arousal thresholds and reduction in cerebral energy consumption (Maquet et al., 1990; Nofzinger et al., 2002). **In this respect, sleep has been described as a form of adaptive inactivity** (Siegel, 2009). The fact that humans sleep at night time fits with this hypothesis as our reliance on daylight vision makes sensory processing at night costly (Hobson & Friston, 2012).

More drastically, prolonged activity has been demonstrated to be deadly. Sleep deprivation experiments during which animals are maintained awake, for example by using electric shocks to prevent them from falling sleep, revealed that a few days of sustained wakefulness leads to death by metabolic and immunological failures (Bergmann et al., 1989; Everson et al., 1989). It has been argued that the dramatic effect of sleep restriction is not tied to sleep privation *per se*, but rather to the stress induced by sleep deprivation protocols (Rial et al., 2007; but see Rechstschaffen & Bergmann, 2002; Rattenborg et al., 2007). Thus, it has been argued that the function of sleep would be nothing but rest. **Being biologically programmed and forced upon organism, sleep would avoid a deadly risk of energy overconsumption by inducing the regular occurrence of a period of inactivity, notably linked to a reduced responsiveness to external stimuli** (Moruzzi, 1969). Following this hypothesis,

unresponsiveness accomplishes an essential function for survival by preventing exhaustion. Homeostasis and disconnection are thus explained and intrinsically linked.

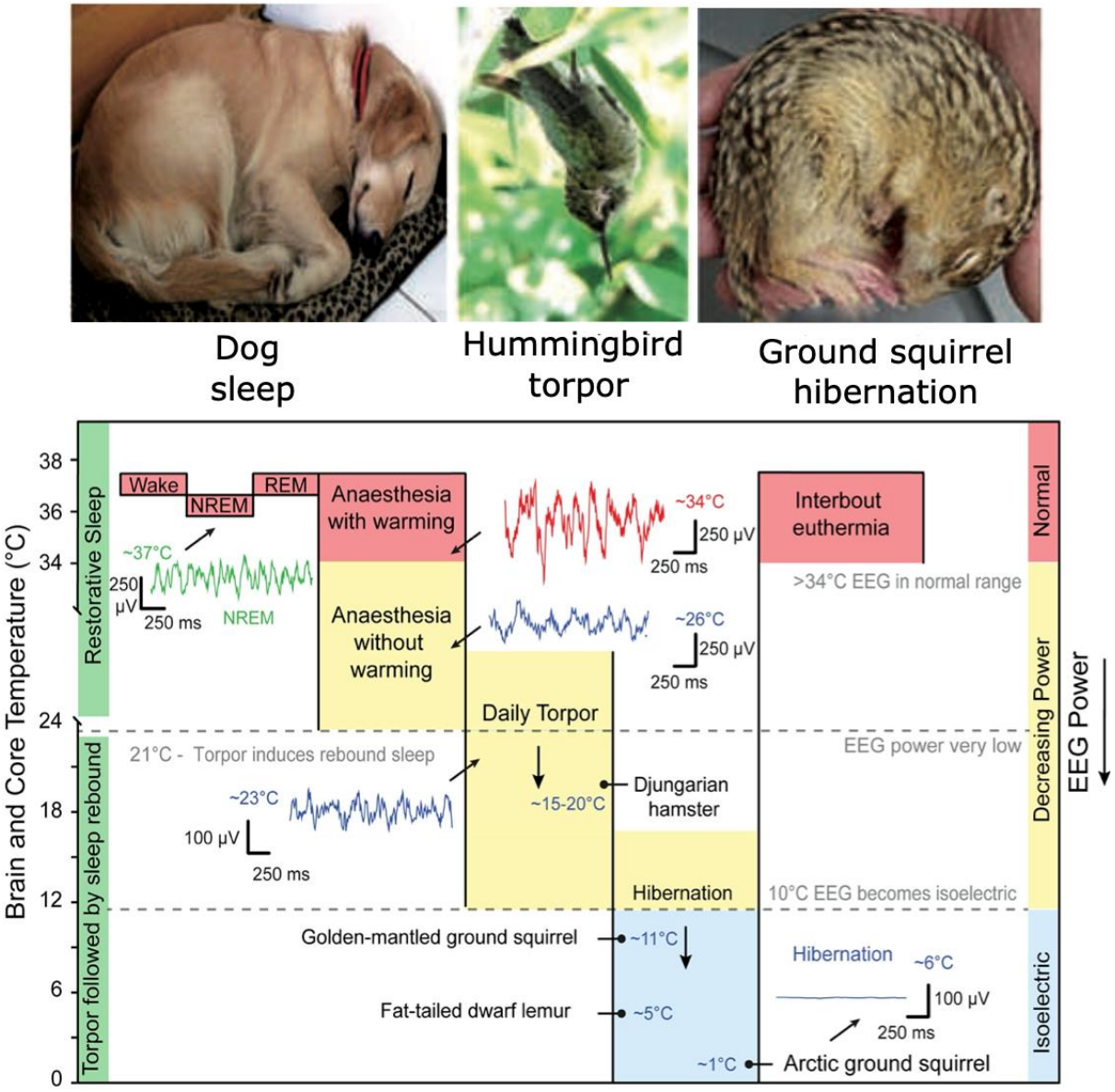


Figure 2 **Regulation of EEG activity and brain temperature in diverse inactivity states.** A continuum is outlined between sleep, torpor and hibernation based on its effects on brain temperature and EEG activity. Torpor is a daily phenomenon associated with food scarcity, while hibernation is a seasonal phenomenon associated with winter survival and reproduction opportunity. Importantly, torpor is followed by a sleep rebound, suggesting that these functions do not involve core features of sleep that are associated with homeostatic regulation. Actually, these functions might come at the expense of sleep in extreme conditions of survival. From Siegel, 2009 and Harding et al., 2019

1.2.2 Disconnection as restoration

Even if sleep and waking rest share behavioral similarities, fundamental differences can be observed upon looking into internal activity. Widespread slow-wave activity is typically observed during sleep but not during rest. Reinforcing the amplitude and occurrence of slow-waves through auditory stimulations in normal sleep benefits immune functions (Besedovsky et al., 2017). SWA present both during sleep and anesthesia has also been related to the metabolic clearance of the brain (Xie et al., 2013). **These evidences indicate that sleep does not passively reduce overactivity during wakefulness. It additionally includes mechanisms that restore awake functions and actively protect from the consequences of prolonged wakefulness.**

Sleep deprivation leads to consequences on the organism and also on cognitive abilities. Attention and memory functions are typically impaired after prolonged wakefulness and are restored after a recuperation sleep (Killgore, 2010). To explain how sleep might serve the homeostatic regulation of cognitive functions, Tononi and Cirelli have proposed the synaptic homeostatic hypothesis (SHY) (Tononi & Cirelli, 2003). **By reducing synaptic strength during sleep and resetting it at a baseline level, the metabolic needs associated with neural functioning are reduced and the efficiency of synaptic transmission is enhanced** (Figure 3A). Slow waves have been proposed to play a key role in this process (Tononi & Cirelli, 2003).

In support to this hypothesis, activity in specific brain networks during wakefulness results in an amplification in SWA over the same brain region during the subsequent night (Huber et al., 2004). Conversely, less active brain regions present lower SWA during the subsequent night (Huber et al., 2006). Using a sleep deprivation protocol, a build-up of SWA can be observed even during wakefulness while recovery sleep was associated with a gradual decrease in SWA (Vyazovskiy et al., 2011; Figure 3B). This highlights SWA as a marker of homeostatic processes associated with activity in wakefulness and restoration during sleep. SWA is characterized by synchronized periods of neural silencing (Steriade et al., 1993; Figure 3B). **After prolonged wakefulness, the intrusion of neuronal silencing in brain networks supporting sensory processing has been causally related to a drop in cognitive performance in response to stimuli** (Nir et al., 2017). The presence of sustained SWA would thus cause the disruption of the cognitive processes supporting the behavioral responsiveness to external stimuli during sleep. Sleep disconnection is thus here a consequence of the brain processes involved in sleep homeostatic functions.

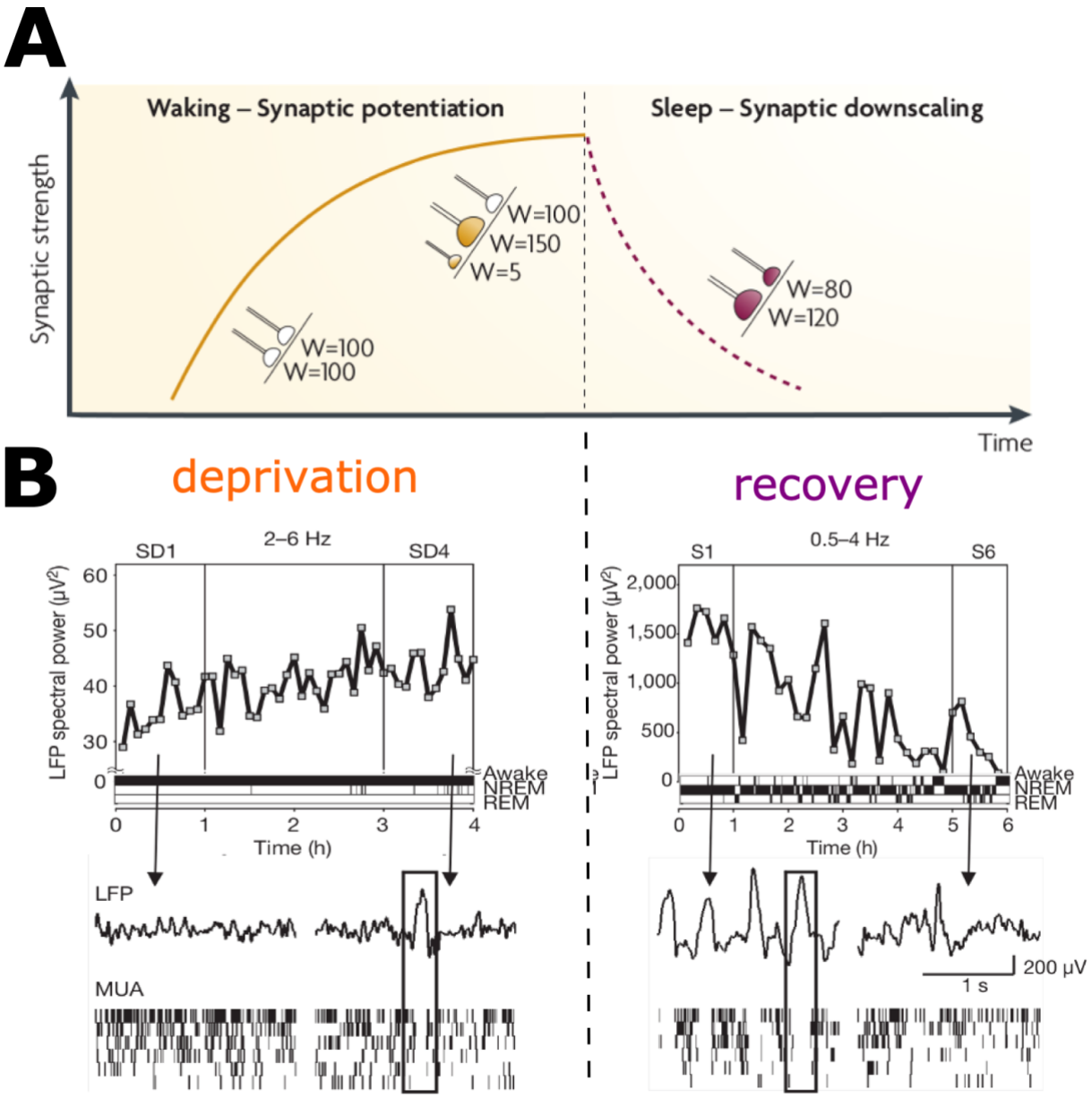


Figure 3 **Synaptic homeostasis hypothesis**. (**A**) Schematic evolution of synaptic strength across one wake-sleep cycle. Awake activity is tied to the potentiation of certain synapses which supports learning. During sleep, the strength of synapses is uniformly reduced. The global synaptic strength is normalized at a baseline level (here W=100). Weak synapses are eliminated while the relative strength of remaining synapses is preserved. From (Diekelmann & Born, 2010) (**B**) Homeostatic regulation of brain activity during and after sleep deprivation in rats. Prolonged wakefulness leads to the increase of low-voltage activity and the presence of concurrent periods of neural silencing in cortical activity. These electrophysiological events manifest the intrusion of sleep like patterns during wakefulness. Conversely, SWA activity is reduced over the course of the recovery night, demonstrating the link between SWA and homeostatic processes. LFP, local field potential; MUA, multi-unit activity. From Vyazovskiy et al., 2011

1.2.3 Disconnecting as reprocessing

Other functions may opportunistically benefit from sleep disconnection. Secretion of certain hormones are increased during sleep, e.g. the growth hormone (GH) (Takahashi et al., 1968). GH has a synergic effect on the selection of immunological cells. Yet, GH secretion is not consistently associated with SWA across the life span (Feinberg, 2000). It is actually rather associated with sleep onset rather than SWA per se (Born, 1988). **Moreover, GH levels are not elevated when slow waves are enhanced with auditory stimulations** (Besedovsky et al., 2017). This suggests that GH secretion benefits from sleep rather than being tied to the specific occurrence of SWA. The action of GH would be indeed optimally performed during sleep, since anti-inflammatory stress hormones active in wakefulness inhibit immune selection (Besedovsky et al., 2012).

Similarly, memory functions have been proposed to opportunistically benefit from the reduction of sensory inputs during sleep (Buszaki, 1989; see Mednick et al., 2011 for a review). It was first proposed that sleep disconnection would help memory recall by reducing the amount of new memories formed during sleep that could interference with pre-existing memory traces (Jenkins & Dallenbach, 1924). Yet, sleep also protects memory from interferences occurring after awakening. This process, called memory consolidation, relies on the transfer of memory traces temporarily encoded in hippocampal activity to the cortex (McGaugh, 2000; Rasch & Born, 2013, Figure 4A). **Models predict that consolidation would be optimally performed "offline", that is in absence of sensory inputs that can alter memory traces during this transfer** (McClelland et al., 1995). It is supported by the synchronized activity of brain rhythms between hippocampal ripples, thalamo-cortical spindles, and cortical slow waves (Peyrache et al., 2009; Staresina et al., 2015, Figure 4B). While memory consolidation also happens during waking rest, it would optimally benefit from the sensory disconnection of NREM sleep.

REM sleep has also been demonstrated to be beneficial for memory reprocessing, especially at the emotional level (Walker & van der Helm, 2009; Boyce et al., 2016), as well as for creativity (Wagner et al., 2004). A continuity between wakefulness and dream has been proposed insofar as dreams would consist in an intensified form of mind-wandering (Fox et al., 2013). Similarly, as dreams, mind-wandering has been associated with emotional memory processing and creativity (Baird et al., 2012; Killingsworth & Gilbert, 2010). Yet, during wakefulness, mind-wandering leads to behavioral impairment (Smallwood et al., 2007). **Memory reprocessing and creative thinking happening during REM sleep would thus be optimally performed when the brain is**

disconnected as they could lead to behavioral deficits if performed during wakefulness.

Disconnection is central in the realization of sleep functions, explaining why it has been selected during evolution. In the following section, we thus hypothesize that sleep disconnection can be informative regarding the sleep process. We will study variations of vigilance defined as the ability to have sustained attention towards external signal and potential threats (Oken et al., 2006). Vigilance can be broken down as a process involving:

- Stimulus encoding, allowing to detect external signals
- Stimulus selection, allowing to prioritize informative signals
- Stimulus integration, allowing to track regularities and discontinuities in sensory information

We will limit the scope of our investigation to human sleep.

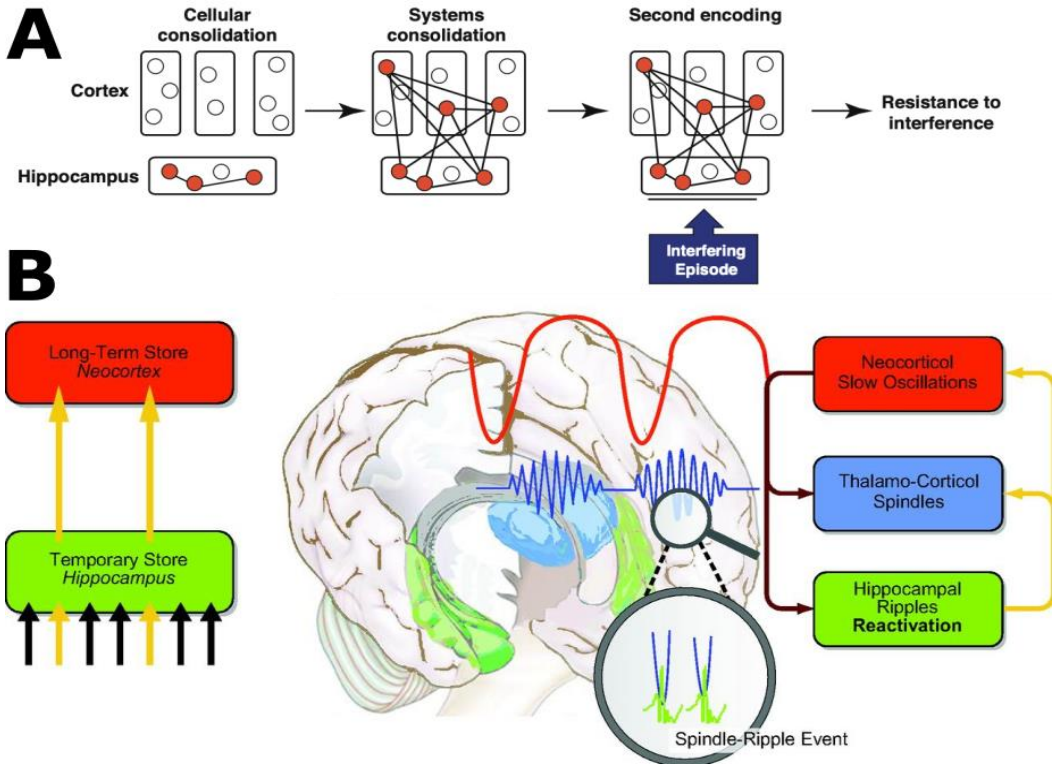


Figure 4 **System consolidation during NREM sleep.**

(**A**) Schematic model of memory consolidation. During wakefulness, cellular consolidation, i.e. the reinforcement of synaptic strength forming a memory trace, ensure the storage of memory traces. During sleep, traces stored in the hippocampus are transferred to the neocortex, forming a trace that is resistant to interferences. Adapted from Mednick et al., 2011

(**B**) Oscillatory correlates of the hippocampal-thalamo-neocortical dialogue supporting systems consolidation. A hierarchical nesting of oscillation allows the effective synchronization of brain regions involved in the transfer of memory information. From Rasch & Born, 2013

1.3 The structure-function of sleep disconnection

1.3.1 Sensory detection

First investigation of sleep disconnection showed that louder sounds are needed for waking up a sleeper in the beginning of the night as compared to the end of the night (Kohlschütter, 1863; Basner, 2010). **Elevated arousal threshold was hypothesized to be associated with the restorative functions of sleep** (Michelson, 1899) **and was typically associated with SWA** (Rechtschaffen et al., 1966). Periods of elevated arousal thresholds during sleep have been referred to as deep sleep, while periods during which it is easier to wake up the sleeper have been called light sleep. A division of labor between light and deep sleep has been proposed. While deep NREM sleep, also called slow-wave sleep (SWS), would thus be rather dedicated to the function of sleep recovery, such as synaptic downscaling, light NREM sleep would be dedicated to more opportunistic functions of sleep such as memory consolidation and dreaming activity, linking thus the realization of sleep functions to variations of vigilance (Genzel et al., 2014).

A similar division of labor for REM sleep has been recently proposed (Simor et al., 2020). REM sleep contains period of eye movement activity called phasic REM sleep (pREM). pREM has been associated with enhanced and more vivid dreaming activity, as compared to periods devoid of eye movements called tonic REM sleep (tREM) (Berger & Oswald, 1962; Goodenough et al., 1959; Molinari & Foulkes, 1969). Arousal thresholds are elevated in pREM as compared to tREM (Price & Kremen, 1980; Ermis et al., 2010). **Thus, it was proposed that tREM would favor sensory alertness while pREM would favor inner processes at the expense of sensory processing** (Simor et al., 2020). Accordingly, neuroimaging revealed that responses to sounds were conserved in tREM sleep but reduced in pREM sleep (Wehrle et al., 2007). Distinguishing between pREM and tREM shows the importance of taking into account micro-physiology to go beyond classical sleep stage classification when studying sleep disconnection.

During NREM sleep, sensory stimulations are known to elicit K-complexes, a large deflection in cerebral activity within the thalamocortical network (Davis et al., 1939; Bastien & Campbell, 1992; Figure 5). A K-complex consists in an early activation of sensory areas, called an up-state, that is associated with sensory encoding (Figure 5). Then, a large negative deflection called a down-state follows and is associated with the silencing of cortical neurons (Cash et al., 2009). Finally, a second up-state is observed and promotes information processing (Halász, 2005). K-complexes differs

from slow waves insofar as down states are isolated during K-complexes while they alternate with up states during slow waves (Cash et al., 2009). **During slow waves, sensory processing critically depends on the timing of stimulation with the ongoing phase of the slow oscillation.** Indeed, stimuli played during up-states are encoded in cortical activity and can boost memory consolidation (Shimizu et al., 2018; Göldi et al., 2019). Conversely, stimuli played during down states are unreliably processed and fail to influence memory consolidation (Schabus et al., 2012; Batterink et al., 2016). Additionally, sleep spindles, a fast-oscillatory thalamo-cortical activity in the 12-16 Hz range, have been involved in processes of memory consolidation (Schabus et al., 2004; Cairney et al., 2018). Spindles have been associated to an enhanced tolerance to external sounds and reduced auditory processing (Dang-Vu et al., 2010; Schabus et al., 2012). External stimuli thus affect internal sleep processes but this effect crucially depends on the presence of micro-physiological markers of sleep functions.

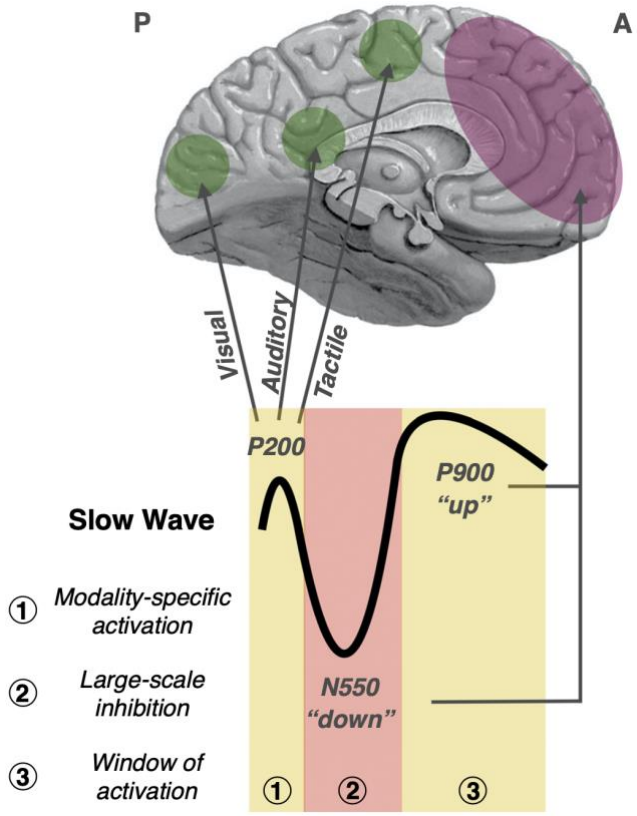


Figure 5 **NREM slow waves and sensory decoupling**. Slow waves can be spontaneous or evoked by sensory stimuli. First, a positive deflection, P200, is found in the sensory areas involved in stimulus processing (e.g. auditory cortices for sounds). A widespread negative deflection (N550 or downstate) follows with maximal amplitude over frontal cortices. Then, after the down-state, a period of cortical activation follows in frontal regions (P900). A: anterior, P: posterior. Highlighted regions (green and purple) are illustrative location of visual, auditory, somatosensory (green) and frontal (purple) cortices. From Andrillon & Kouider, 2020

1.3.2 Sensory selection

Some stimuli are typically more effective to wake up the sleeper, such as one's own name or the cry of one's own child (Oswald et al., 1960; Formby, 1967; Langford et al., 1974). Brain potentials reveal that processing during sleep can be actually quite complex, encompassing preferential processing of emotionally salient stimuli, semantic and lexical categorization, and the detection of auditory, semantic and arithmetic violations (Table 2 for a review of evidence based on EEG, for fMRI see for example Portas et al., 2000). Crucially, these types of processing were mostly found in light NREM sleep and REM sleep but not in deep NREM sleep (Table 2). Only familiarity and emotional salience seem to be preserved across all sleep stages. This suggests that only automatic processes of stimulus discrimination remain in deep sleep. This view is buttressed by the fact that neural correlates of semantic categorization during deep NREM sleep are conserved only if played stimuli had been categorized previously by the sleeper whilst awake (Andrillon et al., 2016). **Thus, stimulus selection appears flexible during light NREM sleep and REM sleep while only automatic processes remain in deep NREM sleep**.

Table 2 **Overview of event-related EEG study of selective auditory processing during sleep**. MMN, Mismatch negativity; P3, Positive deflection at 300ms; N400, Negative deflection at 400 ms; P600, Positive deflection at 600ms; LRP, Lateralized readiness potential

Cognitive processes	**Familiarity/ novelty detection**	**Emotional salience**	**Linguistic categorisation**	**Expectation violations**
Stimulus type (brain markers associated) (references)	Oddball (P3) (Bastuji et al., 1995; Nordby et al., 1996) Own name (P3 and spectral response) (Blume et al., 2017; Perrin et al., 1999)	aversive stimuli (K-complex, delta activity) (Arzi et al., 2014; Canales-Johnson et al., 2020; Williams et al., 1966) angry voice and familiar voice (spectral response) (Blume et al., 2017, 2018)	Semantic and lexical decision (LRP) (Andrillon et al., 2016; Kouider et al., 2014)	Auditory (MMN, P3) (Nielsen-Bohlman et al., 1991; Atienza et al., 2001; Ruby et al., 2008) semantic (N400) (Brualla et al., 1998; Perrin et al., 2002; Ibáñez et al., 2006) arithmetic (N400, P600) (Strauss & Dehaene, 2019)
Sleep stage	NREM and REM sleep	Light NREM and REM sleep	Light NREM sleep; deep NREM and REM sleep for items trained awake	Light NREM and REM sleep

Yet, studies investigating responses to expectation violations showed also that semantic processing differ across wakefulness, light NREM sleep and REM sleep (see Bastuji et al., 2002 for a review). To better understand the factors that determine selective processing across vigilance states, Andrillon and colleagues quantified internal activity with a complexity measure correlating with conscious processing during both wakefulness and sleep (Andrillon et al., 2016; Schartner et al., 2017). Baseline complexity before stimulus presentation was found to correlate positively with neural markers of semantic categorization during wakefulness and light NREM sleep, meaning that enhanced complex cerebral activity favors selective stimulus processing during both vigilance states (Andrillon et al., 2016). Nevertheless, the inverse relationship was found during REM sleep. **This suggests that enhanced complex cerebral activity, supposedly reflecting dreaming activity, gates selective processing in REM sleep**. In line with this hypothesis, selective responses to deviant stimuli are reduced in pREM as compared to tREM (Sallinen et al., 1996). A decrease in higher-order selective processing is observed in both NREM sleep and REM sleep, and depends crucially on the presence of micro-physiological markers of internal activity.

How micro-physiology impacts selective processing of external information is still unclear. Using a cocktail party situation, Legendre and colleagues investigated selective processing during NREM sleep (Legendre et al., 2019). Meaningful and meaningless speech were played simultaneously in each ear while subjects were instructed to focus exclusively on meaningful speech before falling asleep. Once asleep, they found that the encoding of both speech streams was conserved during light NREM sleep. Yet, at the moment of K-complexes, both streams were suppressed and a regain of selective processing was observed only after K-complexes. This reflects a suppression of external processing during down states followed by a promotion of selective processing during the following up state. **In comparison, slow waves were associated with a selective suppression of informative speech that was followed by a lack of selective processing.** This illustrates how different micro-physiological events during sleep can be associated with the selective gating, or conversely, the selective amplification of sensory information.

1.3.3 Sensory integration

Integration of sensory information at multiple time scales relies on memory. The detection of the violations of auditory and semantic regularities involves short-term memory and is largely preserved during both light NREM sleep and REM sleep (Bastuji et al., 2002). Yet, using longer sentences and in presence of surrounding noise, the detection of semantic deviants in light NREM

sleep is reduced, showing that the maintenance of relevant information relying on working memory is altered during sleep (Daltrozzo et al., 2012). Similar results were obtained in REM sleep as raising the intervals between stimulations prevented the detection of deviant stimuli (Atienza et al., 2001). How words are integrated into sentences during sleep has also been investigated using neuroimaging but failed to demonstrate the emergence of neural processing of linguistic units beyond simple acoustic regularities (Makov et al., 2017). **This negative result is in line with further evidence showing that the hierarchical auditory processing on longer time scales is impaired during sleep** (Strauss et al., 2015; Farthouat et al., 2018). Overall, these results suggest that short-term memory is preserved but working memory that supports the tracking of high-level temporal dependencies is impaired during sleep.

During SWS, detection of auditory deviations is abolished (Nielsen-Bohlman et al., 1991). Periods of neural silencing during down states of slow waves have been identified as preventing the integration of information across time and among brain regions (Esser et al., 2009; Pigorini et al., 2015). This loss in the causal flow of information is thought to underlie the decrease of consciousness in SWS (Tononi & Massimini, 2008). Moreover, SWA is strongest over frontal region (Massimini et al., 2004) thought to play a key role in working memory and consciousness (Owen et al., 1990; Dehaene, 2014). In REM sleep, prefrontal regions are also deactivated, despite preserved conscious processing associated with dreaming activity (Maquet et al., 1996). **Deficit in executive functions supported by prefrontal regions might coherently explain the deficits in information integration in NREM sleep and its reduction in REM sleep**. Yet, by training on a task whilst being awake and playing the same stimuli during sleep, sensory integration at long time scales was preserved in REM sleep, showing that automatic processes allow for the integration of sensory information and selective processing during sleep (Atienza & Cantero, 2001).

Studies also investigated long-term memory formation during sleep but yielded mostly negative results (Peigneux et al., 2001). **Yet, a growing number of studies over the past years demonstrated that memory formation can be evidenced during sleep** (see Table 3 for an overview, but see also e.g., Farthouat et al., 2018 for negative evidence in a perceptual learning paradigm). Investigating perceptual learning during sleep in a sensory detection task, Andrillon and colleagues found that stimulus detection was suppressed during NREM sleep but enhanced during REM sleep (Andrillon et al., 2017). These effects are coherent with the complementary roles proposed for NREM and REM sleep regarding memory processing, a hypothesis called the sequential hypothesis (Giuditta et al., 1995).

Table 3 **Studies demonstrating sleep learning in humans.**
EEG ERP – EEG event-related potentials; HR – heart rate; W – waking; "–" indicates absence of learning effect; "±" indicates learning effect limited or weak; "+" indicates presence of learning effect; ">" indicates learning effect more marked in one state than another. Adapted from Puchkova, 2020 and completed with two additional studies

Learning	Stimulus	Reaction	Learning	Notes	Reference
discrimination of sounds	Speech sounds	EEG ERP	W+ Sleep+	Neonates. Additional learning during sleep	(Cheour et al., 2002)
Associative	Sound/puff of air on eyelid	Eyelid movement		Neonates. Reactions and learning during sleep only	(Fifer et al., 2010)
	Sound/electric shock	Change in HR	N2+ N3+ N3 > N2		(Ikeda & Morotomi, 1996)
	Sound/odor	Volume of inhalation	REM– NREM+	During sleep, reaction in REM > NREM	(Arzi et al., 2012)
	Odor of cigarette /odor	Cigarette consumption	W– REM+ N2+ N2 > REM		(Arzi et al., 2014)
	Sound/odor	Volume of inhalation, EEG rhythms	NREM+	Growth of δ and σ rhythms in NREM to "unpleasant" odor	(Canales-Johnson et al., 2020)
	Word/ pseudoword	Categorization, EEG ERP, spectral change, slow-wave phase, fMRI activation	N3+	memory is predicted by evoked SWA during sleep and hippocampal activation at retrieval	(Züst et al., 2019)
Perceptual	Looped sound segments	Evoked EEG activity, detection of stimuli in noise	W+, REM+ NREM± N2 > N3	In the morning – weakened memory for stimuli previously presented in NREM	(Andrillon et al., 2017)
Perceptual recognition, old/new	Words, pseudoword	Recognition of old stimulus, confidence in recognition, EEG ERP	W+ Sleep±	Implicit memory affects EEG ERP and confidence in recognition of words	(Andrillon & Kouider, 2016)
Perceptual and semantic priming	Words	EEG ERP, volume for stimulus identification in noise, response time for perceptual categorization	NREM±	No main effect but correlation between ERP during sleep and perceptual and semantic priming performance	(Ruch et al., 2014)

While NREM would be associated with the weakening of memory traces, REM sleep would be associated with their integration into existing memory representations. This suggests furthermore that the memory function supporting sensory detection depends crucially on the internal processes occurring during sleep.

Following this analysis, we will investigate in this thesis how different components of sensory processing supporting vigilance depend on sleep internal activity. To do so, we will test three hypotheses:

1) Semantic associations can be learned during light NREM sleep and REM sleep (**study 1**)
2) Informative speech can be selectively processed during tonic REM sleep, but would be selectively suppressed during phasic REM sleep (**study 2**)
3) Sensory integration can be maintained across slow waves when the task is automatized (**study 3**)

In the absence of behavior, these studies necessitate the development of experimental approaches that bypass the active participation of subjects. To do so, decoding techniques of neural activity of sensory processing will be developed. Additionally, physiological markers of sleep activity will be taken into account to study how the ongoing sleep processes play a role in the covert processing of sensory signals during sleep.

2 GENERAL METHODOLOGY

In this section, we will introduce the methodology developed to answer these scientific questions. Indeed, sleep disconnection raises a methodological challenge. In the absence of overt behavior, neurophysiological measurements can circumvent sleep disconnection and give a direct insight into the internal activity of the sleeper and its responses to external stimulation. Going one step beyond, by modelling both the neural activity of the sleeper and controlling the stimulation using a brain-computer interface, one can directly interact with the sleeping brain and dynamically target defined windows of the sleep internal processes.

"An ajar door, from which the chords of a music reaches us, that in this place seems to us unreal"
IAM – The empire of the dark side

Illustration from the Poster Brunch session – "reconnecting with our dreams" – Science/Art project with Dance Me Deep (2020) (©Grégoire Romanet)

2.1 Experimental procedure

2.1.1 Task and stimuli

To test our hypotheses, we designed three experimental studies. In study 1, we aimed at investigating whether semantic associations can be formed during sleep and transferred from the auditory to the visual modality at awakening. To do so, we selected Japanese words and associated them with a characteristic sound (e.g., *inu* for dog and a dog barking "woof") and a corresponding image (a picture of a dog). Sounds were first paired with images during wakefulness (e.g., a picture of a dog with the sound "woof"). Then, during sleep, Japanese translations were played simultaneously with their corresponding sounds (e.g. "*inu*" for dog with the sound "woof"). Recall for these associations was tested at awakening. Japanese words were played accompanied by two pictures and participants had to choose which one corresponded to the Japanese word (e.g. "*inu*" with the picture of a dog and the picture of a bell). Additionally, different sets of associations were played during NREM and REM sleep.

In study 2, we aimed at investigating whether speech was selectively processed during REM sleep. To do so, participants were exposed simultaneously to two different stories, one being in French in one ear and the other in a pseudo language, called Jabberwocky, in the other ear. Jabberwocky stories were similar to French except for content words (e.g. nouns, verbs) that were replaced by words that respected French phonology but were completely meaningless. Thus, we created a situation where two competing speech streams were matched in acoustic properties but differed in their semantic content. First at wake, participants were asked to focus exclusively on French stories while ignoring completely Jabberwocky stories. Then, participants were allowed to fall asleep for a morning nap while new stories were continuously played. We relied on a neural decoding approach to track the processing of each speech stream across vigilance states.

In study 3, we aimed at investigating whether sensory information was maintained across slow waves. To do so, participants were asked to detect the regular repetition of a target tone while other competing irregular tones were simultaneously played and masked the target. A valid cue preceded one half of the trials and was composed of target tones without the masker in order to facilitate the subsequent detection of the target. In the other half of trials, the cue was invalid and was composed of tones that were different from the target. We designed these stimuli to fit the time scale of a slow wave, i.e. around 1 second. Participants first trained on the task whilst

being awake. Trials were continuously played during sleep. Additionally, a brain-computer interface detected the slow waves and different parts of the stimuli were played according to the slow-wave phase. The cue was played during an up state while the target and the competing sounds were played during the subsequent down states and up states.

2.1.2 Experimental settings

All experiments were conducted at the Centre du Sommeil et de la Vigilance of Hôtel-Dieu (Paris). We realized study 1 and study 3 with the same participants during the early-night sleep (study 3) and late-night sleep (study 1). Participants arrived at 10pm. They began the first experiment (study 3) and started the sleep phase around 11pm30. This time period was chosen to fit the average sleeping time and chronotypes of young adults (Lehnkering & Siegmund, 2007). The experiment was terminated around 3am upon spontaneous awakening or when participants entered light NREM sleep stage. This procedure aimed at avoiding sleep inertia, i.e. the difficulty in recovering cognitive abilities upon awakening, that is known to be more pronounced when awakening from deep NREM sleep (Tassi & Muzet, 2000). Light was then switched on and participants started the second experiment whenever they felt ready (study 1). Participants were then woken up at 7am whenever they entered light NREM sleep stages or upon spontaneous awakening. Participants passed the memory test, showered and the experiment was over at 8am.

Study 2 was conducted in the morning in order to reproduce late sleeping. Participants arrived at 7am30. They first performed the task whilst being awake and then were offered a 90-minute nap opportunity, i.e. one sleep cycle. Sound stimulations were continuously played. **Because of failures to fall asleep or awakenings in our experimental conditions, only 43% of our participants reached a sufficient amount of REM sleep for analysis (18 out of 42 participants).** Participants were then awakened whenever they reached light NREM sleep or upon spontaneous awakening and the experiment was terminated.

All protocols were approved by a local ethical committee (Comité de Protection des Personnes Ile-de-France 1). Participants provided informed consent about the experimental procedure. They were first sent the complete description of the protocol before confirming their participation to the experiment. Participants for study 1 and 3 were additionally interviewed by a sleep doctor one week prior the experiment to ensure good health, normal hearing and no history of sleep disorders (Figure 6). **During the experiment, the volume of stimulations during sleep was adapted**

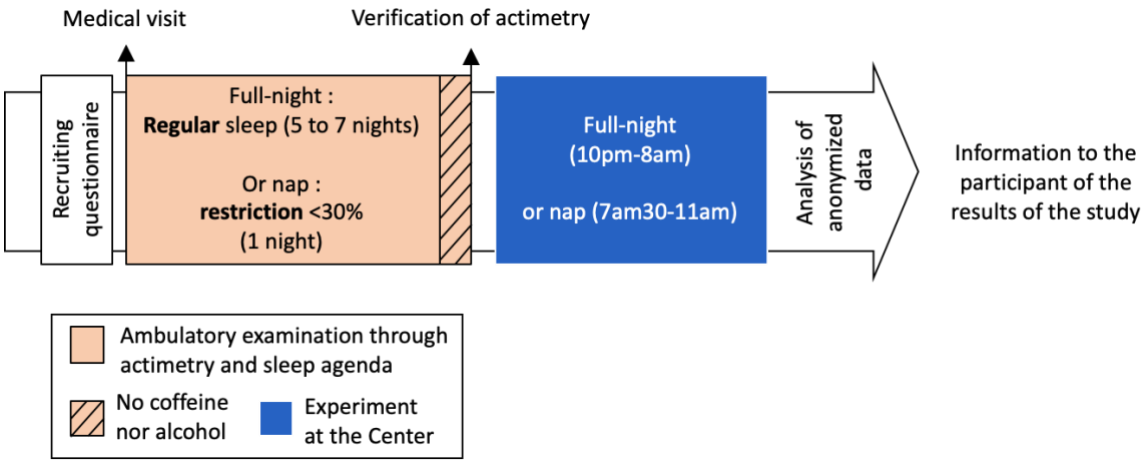


Figure 6 **The stages of the protocol for nap or full-night paradigms.** Participants could be excluded from the study at the stages indicated by arrows. Indeed, if participants had prior history of sleep disorders or other non-equilibrated pathological conditions, they could not participate to the study. They were also excluded if they did not comply with sleep restriction for the nap study, or did not have regular sleep habits the week before the experiment for the full-night paradigm.

according to participants' preferences. At the end of the experiments, participants were paid 60 (study 2) or 100 euros (study 1 and 3). Data were conserved in an anonymous manner. Study results were shared with participants at the end of the study and at the moment of publication.

2.1.3 Participants

Participants of our studies were selected based on online questionnaires. They were selected according to their age (18-35 years). Indeed, cognitive processes such as attention and memory are less performant and more variable with aging (Harada et al., 2013). Sleep quality also decreases and sleep patterns become less stable (Mander et al., 2017). **Additionally, participants were selected if they could easily fall asleep even in unfamiliar environment and in the presence of sounds**. Participants with high anxiety and depression scores, i.e. below 11, assessed by the Hospital Anxiety and Depression scale (HAD) were excluded (Zigmond & Snaith, 1983). Anxiety and depression might indeed involve changes in cognitive performance and have been linked to sleep perturbations (Alvaro et al., 2013). Moreover, stressed participants as assessed by scores above 20 at the Ford test were excluded from the studies (Chen et al., 2015). Finally, participants that presented excessive sleepiness, i.e. scores above 16 on the Epworth scale, were excluded as it could be indicative of an underlying sleep pathology (Johns, 1991). Sleep habits were also collected and taken into account (Table 4).

Table 4 **Sleep habits questionnaire complementing standardized questionnaires**

Usually, when do you go to bed during the week?	**1) 20h-22h, 2) 22h-0h, 3) 0h-2h, 4) 2h-4h**
Usually, when do you wake up during the week?	1) 4h-6h, 2) 6h-8h, 3) 8h-12h, 4) 12h-14h
How many hours do you sleep on weekdays?	
How many hours do you sleep on weekends (without constraints on waking up the day after)?	
What is your degree of tiredness during the week?	On a scale from 1 (alert, not tired at all) to 10 (somnolent, very tired).
Usually, how much time is required for you to fall asleep? (in minutes)	
On average, how many times do you wake up at night?	
If you wake up, is it easy to go back to sleep?	On a scale from 1 (not easy at all) to 10 (very easy).
Do you regularly nap? If so, at what time?	
To fall asleep, what is your sensitivity to the place where you are (unfamiliar place, train, hostel...)?	
To fall asleep, what is your sensitivity to external sounds?	On a scale from 1 (not sensitive at all) to 10 (very sensitive).

We assessed the chronotypes of subjects based on the Morningness-Eveningness questionnaire (Horne & Ostberg, 1976). For the nap study (study 2), participants with normal or late chronotypes, i.e., scores between 42 and 30, were selected for ensuring their propensity to fall asleep in the morning.

Additionally, for morning naps, night sleep before the experiment was restricted to about 70% to increase their sleepiness. This procedure triggered sufficient REM sleep pressure without having drastic consequences on the cognitive abilities of the participants the day of the experiment (Tinguely et al., 2006). **They were monitored through actimetry and filled a sleep agenda the day before the experiment to ensure that they respected time constraints**. Concerning full-night paradigms (study 1 and 3), monitoring through actimetry and sleep agenda was extended on 7 days to ensure regular sleep habits the week before the experiment. Participants were additionally

asked from refraining consuming alcohol and caffeine the day of the experiment to prevent them from staying awake. Failing to comply of compliance to this procedure led to the exclusion of the study.

2.2 Studying sleep physiology

2.2.1 Neuroimaging of sleep cognition

The scientific definition of sleep in humans relies on the neurophysiological assessment of brain activity with electroencephalography (EEG), of the movements of the eyes by electrooculography (EOG), and of the muscular activity of peripheral systems through the use electromyography (EMG) (Iber et al., 2007). Chin EMG is chosen as a conservative estimate of REM sleep as it is the last part of the body where muscular activity is decreased in REM sleep. **EOG is additionally used to detect eye movements occurring during REM sleep.** EEG records brain electrical activity at the surface of the skull in a non-invasive manner (Berger, 1929; Figure 7A).

Because the strength of an electrical signal is inversely correlated to the squared distance separating its source and the recording site, EEG captures only the activity coming from the superficial part of the brain called the cortex (Figure 7B). The cortex is composed of a dense network of neuronal projections along which the propagation of electrical signals causes extracellular currents of electrical charges. The current generated is proportional to the number of active neurons. Thousands or tens of thousands of neurons are necessary to produce a signal strong enough to be recorded at the surface of the skull. Another factor adds up to this limitation. The electrical signal is modified by diffusion through different bodily layers that cover and protect the brain (Figure 7B). **Because of its weak spatial resolution, we do not interpret EEG as providing us precise neurophysiological underpinnings of the cognitive activities that are investigated**.

Rather, we use EEG to identify markers of cognitive activity. Thus, we restrict our recordings to 64 sensors distributed over the skull to image cerebral activity with a resolution good enough to identify and decode the different patterns of activity across cortical regions. The sleep internal processes and the cortical processing of sounds can thus be recorded across a large portion of the brain. Additionally, EEG present less constraints regarding the study of sleep in comparison to other neuroimaging techniques such as functional magnetic resonance imaging (fMRI) or magnetoencephalography (MEG). Indeed, fMRI and MEG are voluminous and fMRI is additionally noisy which makes it susceptible to wake up the sleeper. **Finally, EEG has an excellent temporal resolution as compared to a fMRI technique, allowing to capture the neural processes dynamics occurring during sleep**. Thus, the choice of high-density EEG is adapted for the study of sleep cognition and sleep physiology.

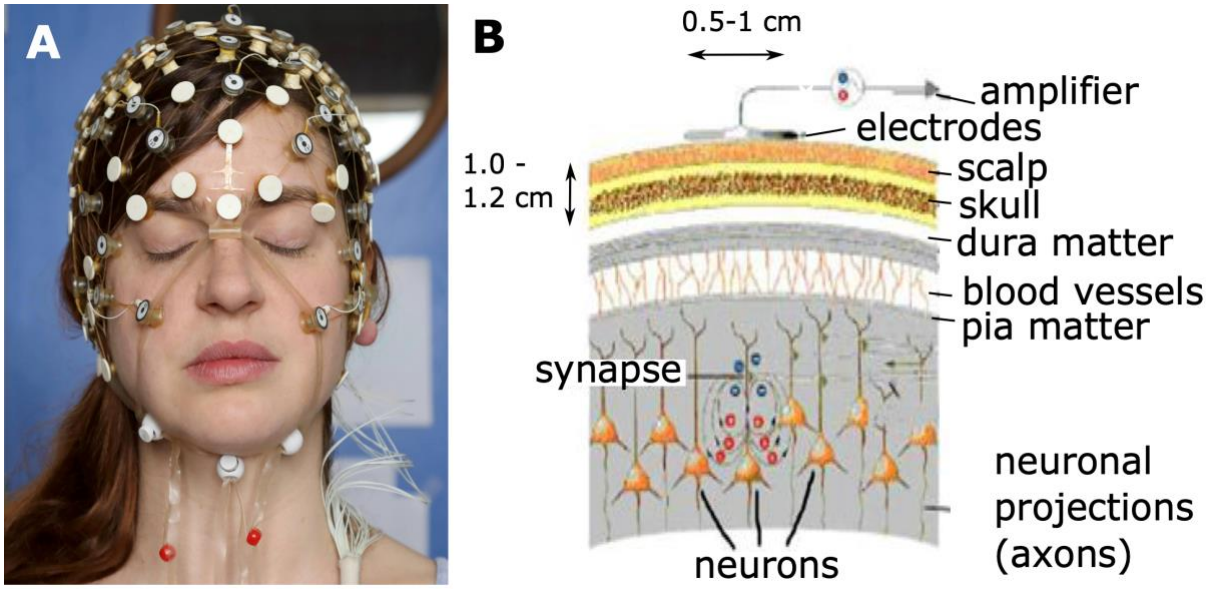


Figure 7 **High-density EEG: example and principle.**

A. 64-electrodes headset displayed on a participant © Justine Emard

B. Synaptic activity and neuronal propagation along neuronal projections within cortical layers result in ion currents in the extracellular space. Electromagnetic fields generated by this flux of electrical charges is recorded at the surface of the scalp after its diffusion by volume conduction through the different layers separating the electrode and the cortex.

2.2.2 Characterizing sleep electrophysiology

Sleep states have been consensually defined based on neurophysiological criteria involving both spectral activity and electrophysiological events (Iber et al., 2007). For example, the presence of K-complexes in a scoring window is indicative of light NREM sleep, also called N2, while the presence of slow waves in a proportion above 20% ranks it as deep NREM sleep, also called N3 (Figure 8). REM sleep is characterized by a desynchronized EEG pattern with a low muscular tonus. Finally, N1 features a mix of wake and sleep patterns with the presence of alpha activity and theta waves. **Since N1 is considered a transitory state, it was excluded from our analyses across all studies and we focused only on consolidated sleep, i.e. N2, N3 and REM sleep.**

Sleep scoring is performed visually. Because interscorer reliability is typically around 80% (Danker-Hopfe et al., 2009), multiple scorers are required to cross-validate sleep scoring. **Additionally, we relied on online scoring to ensure that certain stimuli were played in specific sleep stages**. Only trials for which online scoring was validated by offline scoring were kept for further analyses.

Sleep scoring also presents some limitations. Mental activity is variable within the same sleep stage, since for example dream recall is more frequent during late night N2 as compared to early night N2 (Casagrande et al., 1996). Comparisons of effects for the same sleep stage at different moments of the night might thus be confounded by such factors. **This argues in favor of going beyond sleep stages and relying on specific markers of internal activity to assess internal cognitive activity during sleep.** For example, in study 2, we differentiated between phasic and tonic REM sleep based on the presence of bursts of eye movements although this distinction is not officially recognized by the American Association of Sleep Medicine (AASM) (Iber et al., 2007; Figure 8C).

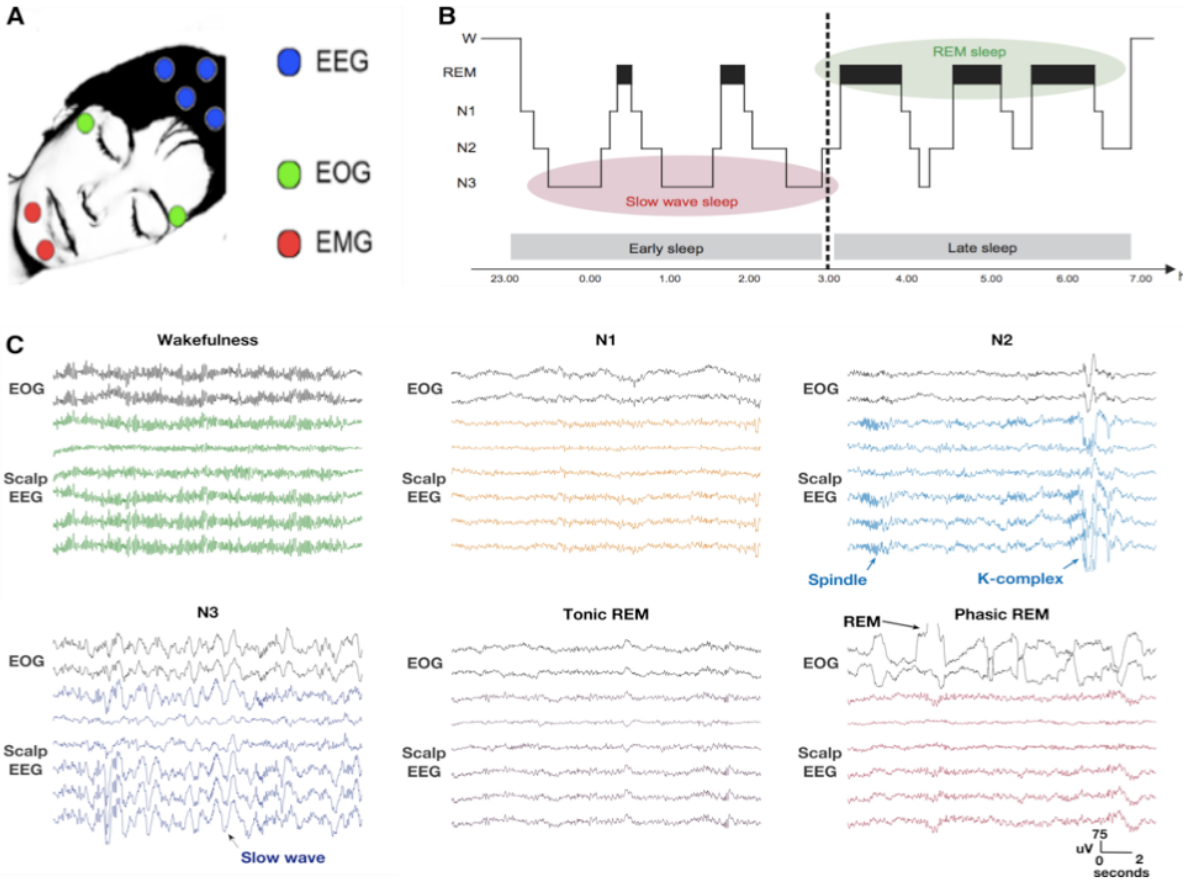


Figure 8 **Polysomnography study of sleep stages across one night**. (**A**) EEG, EOG and chin EMG are used for the neurophysiological assessment of sleep stages. From Nir & Tononi, 2010 (**B**) Example of sleep scoring for one night called a hypnogram. From Rasch & Born, 2013 (**C**) Illustration of the different sleep stages scored according to the AASM manuals with the addition of the tonic/phasic REM sleep distinction (Iber et al., 2007).

2.2.3 Identifying microphysiological activity

The detection of eye movements during REM sleep was based on visual detection by two trained scorers blind to experimental conditions (study 2). Indeed, as there is no amplitude threshold to define eye movements, automatic detection remains sensitive to parameter choices and visual confirmation needs to be performed (Andrillon et al., 2015). For events during NREM sleep, an automatic method was used to detect microphysiological events (Nir et al., 2011)). K-complexes and slow waves in study 3 were automatically detected based on existing algorithms (Nir et al., 2011). Additionally, because we needed to deliver auditory stimulation locked to the phase of slow waves, we developed an in-house algorithm that detects slow waves in real time.

Slow waves are well defined in terms of amplitude (>75 μV), location (over frontal regions) and duration (frequency between 0.5 and 2 Hz) (Iber et al., 2007). This is ideally suited for automatic detection. **To do so, we first investigated the performance of existing algorithms that were developed in the last 10 years** (Table 5). The first published algorithm relied on defining *a priori* an amplitude threshold and a period to both detect and stimulate slow waves according to their phase (Ngo et al., 2013). Yet, because the frequency of slow waves varies across sleep and participants, this method is relatively imprecise to target the phase of slow waves (Santostasi et al., 2016). Methods were developed to adapt the frequency of slow waves in real time by fitting sinusoids of varying frequencies to the EEG signal (Cox et al., 2014). Yet, because the shape of the slow wave may also vary within and across slow waves and is imperfectly modelled as a steady-state sinusoid, a third class of algorithm called phase-locked loop (PLL) was developed to adapt in real time to changes in the shape of slow waves (Santostasi et al., 2016).

We developed an algorithm of this nature in study 3 to fit the objective of this study. Slow waves were detected over the frontal electrode Fz. The detection of a slow wave was based on established amplitude and frequency criteria (Iber et al., 2007). Furthermore, a PPL predicted the period of the slow wave and its phase in real time (Santostasi et al., 2016). Whenever a transition from down-to-up state was detected, the cue was played and its duration was adapted to the period of slow-waves. It was followed by the masker over an entire period. **To the extent of our knowledge, the use of a BCI that adapts both the timing and duration of the stimulation according to slow waves has not been developed yet.** Indeed, the objectives of our BCI system are quite different from previous uses of BCI during sleep, as we aim to investigate the processing of sensory information across a slow wave, rather than targeting one of its oscillatory phases.

Table 5 **Overview of BCI techniques for real-time slow-wave detection.** Phase-locked loop allows to adapt more closely to changes in the form of slow waves, while the sinus fitting methods models slow waves as a steady-state sinusoidal signal.
X : does not compute in real time, O : computes in real-time

	Period	**Shape**	**Notes**	**References**
Fixed threshold and fixed period	X	X	Up- and down-phases are targeted	Ngo et al., 2013
Sinus fitting	O	X	Additional criteria to ensure detection during SWS	Cox et al., 2014; Debellemaniere et al., 2018; Ketz et al., 2018
Phase-locked loop	O	O	Higher performance than fixed method	Santostasi et al., 2016

2.3 Studying sensory processing during sleep

2.3.1 Inducing a task during sleep

Several factors limit *prima facie* the study of sensory processing during sleep. The first is the impossibility to learn a new task during sleep. **To circumvent this difficulty, we relied on a task-induction procedure** (Kouider et al., 2014; Figure 9). Participants first trained on performing the task at wake. The initialization of a novel task necessitates the involvement of executive functions (Diamond, 2013). Yet, repeating the same task allows to perform it automatically and bypass executive functions (Frith & Dolan, 1996). Executive functions are believed to be impaired during sleep as they rely on prefrontal activity (Koechlin & Summerfield, 2007) that is deactivated during REM sleep (Maquet et al., 1990) or disrupted by slow wave activity during NREM sleep (Massimini et al., 2005). Thus, this procedure was used across all our studies to promote auditory processing and target precise cognitive processes during sleep.

In the absence of behavior during sleep, the task induction procedure also allows to identify the neural correlates of the task realization while it is performed being awake (Figure 9). By comparing the neural correlates of stimulus processing and behavioral performance, we can validate that neural markers accurately reflect the cognitive process studied. **They can then be used to interpret cognitive processes during sleep despite the absence of behavior** (Figure 9).

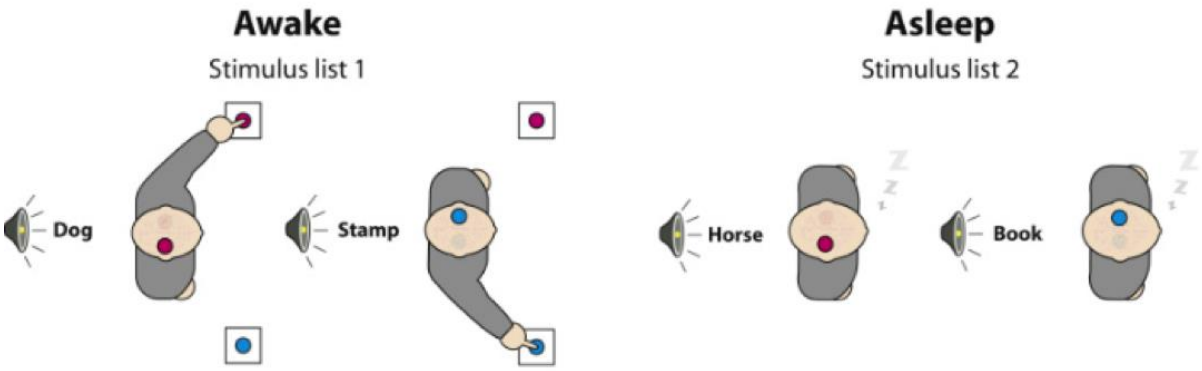


Figure 9 **Illustrative principle of the task induction approach**. In this experiment, the participant had to press a button according to whether the word is an object or an animal. Once asleep, the preservation of the semantic categorization can be studied by looking at the brain correlates of task decision as revealed by a lateralized readiness response over the motor cortex. The presence of these markers can further be compared across vigilance states and in relation to the neurophysiological markers of sleep internal activity. From Kouider et al., 2014

Finally, we followed the task induction procedure by continuously stimulating the participants during the transition to sleep and throughout the whole sleep period. **Doing so allows to maintain sensory processes active upon entering sleep and habituate participants to auditory stimulation in order to reduce awakenings.** Online sleep scoring is used to systematically deliver new stimuli whenever the participant enters a specific sleep phase. Additionally, by continuously stimulating the sleeper, we do not need to precisely target some sleep events. Using the offline identification of sleep patterns and offline analyses of brain responses to sounds, we can investigate how stimulus processing interacts with the sleep internal activity.

2.3.2 Decoding EEG activity in response to sounds

Experiments investigating sound processing during sleep classically rely on waking up the sleeper. Yet, awakening the sleeper has the drawback of interrupting sleep and rendering necessary to wait for the participant to go back to sleep to make further measurements. **By avoiding to wake up the sleeper, ongoing sleep processes can unfold and their interaction with stimulus processing can be studied**. Indirect evidence of sensory processing can be first obtained through studying how stimulation during sleep affects sleep functions. Even without awakening the sleeper, stimuli during light NREM sleep are known to evoke K-complexes (Davis et al., 1939). The induction of sleep internal activity can thus be used as an index of sensory processing.

Auditory processing is also studied by averaging brain responses locked to stimulus onset, a technique called event related potentials (ERP) (Picton, 2010). Because of the low signal-to-noise ratio of scalp EEG, averages over tens to hundreds of trials are needed to obtain a robust estimate of the brain response. **The timing and topography of brain response to stimuli have been identified as neural markers of different stages of sensory processing**. Studying how they are preserved during sleep can be used as evidence of the maintenance of associated cognitive process, e.g. showing that semantic processing is preserved during sleep (Bastuji et al., 2002).

Continuous stimuli also possess dynamical properties such as variations of sound intensity across time or the power spectrum of the sound stimulus. How variations of stimulus properties affect brain activity throughout time can be investigated using EEG as it possesses an excellent temporal resolution. Thus, we relied on a decoding approach in study 2 that maps during wakefulness how the brain follows variations of the speech envelope. **This model of the brain response to sound variations is applied to continuously decode how the brain tracks auditory stimuli across**

vigilance states. For study 3, we extracted the spectral activity from brain signals to investigate whether the neural activity was entrained at the stimulus frequency.

2.3.3 Studying the interaction of sensory processing with sleep processes

To show that auditory stimulations remain processed at the cortical level during sleep, brain response to sounds can be compared to baseline activity. Additionally, brain responses can be compared across different experimental conditions. These different conditions can be linked to the stimulus (e.g., stimulus type) or to sleep internal activity (e.g., sleep stage). **Contrasting conditions across both stimulus category and background states allows to study how the different levels of sensory processing interact with the ongoing sleep activity**.

To study how sensory processing interacts with micro-physiological activity, we investigated in study 1 the propensity of sounds to elicit K-complexes. In study 2, **neural responses to speech were decoded around the onset of eye movements during REM sleep, allowing to characterize the temporal course of sensory processing before, during and after the occurrence of eye movements.** In study 3, our approach was different as we directly controlled the stimulus presentation depending on the presence of slow waves using a brain computer interface.

To reduce our impact on ongoing sleep physiology, we filled interstimulus interval with white noise in study 1 and 3. In study 2, stories were a minute long, with four to six seconds of interstimulus interval. Thus, the sleeping brain was almost stimulated continuously during sleep. By exposing sleepers with the same level of sound intensity across sleep, we aimed at reducing awakenings induced by the detection of novel sensory events and reduce the impact of sensory stimuli on sleep internal processes. Indeed, in NREM sleep, it was demonstrated that slow waves could be amplified or disrupted depending on the timing of the stimulation (Figure 10). **Thus, we hypothesized that continuous sound stimulation would promote that variations in brain signals were related to the processing of the content of the stimuli rather than their presentation.**

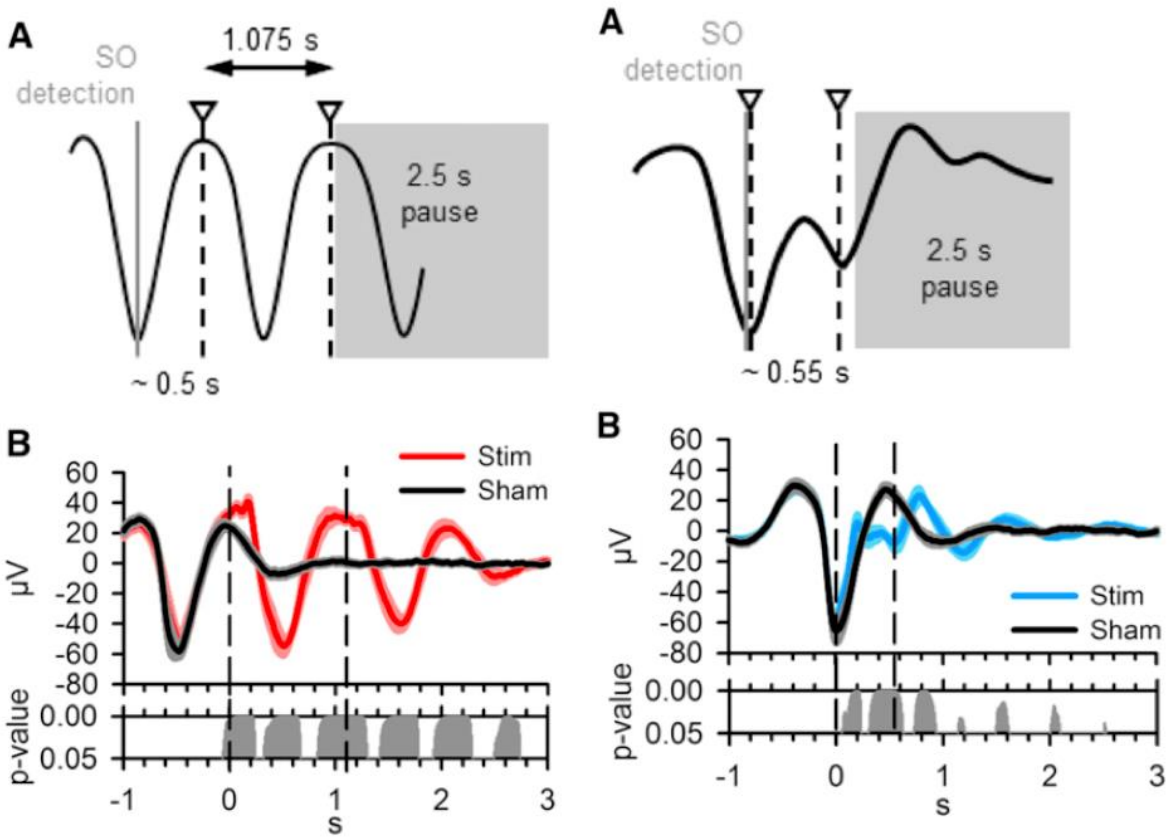


Figure 10 **White noise played in-phase and out-phase differently impacts slow wave activity**. (**A,C**) Schematic detection and stimulation of slow waves in (A) or out of phase (B) (**B,D**) Enhancement (B) or deterioration (D) of slow-wave activity following sound stimulation in-phase (B) or out-of phase (D). EEG signal locked to stimulation is averaged for each participant over Cz. Mean and SEM across participants are represented. SO, slow oscillation; Stim, stimulation, Sham, no presentation. Dotted lines represent sound stimulations. Grey shadings represent statistical p-values for the difference of potentials between the stimulation and the sham condition. From Ngo et al., 2013

RESULTS

In this section, we will present three studies I have conducted during this PhD.

STUDY 1 interrogates to what extend we can form **new associative memory** for the meaning of foreign (Japanese) words **during late night sleep**.

STUDY 2 investigates **selective processing during REM sleep** and its dependence on the presence of markers of internal activity, namely rapid **eye movements**.

STUDY 3 develops a brain-computer interface for the study of **selective processing and integration of information across different phases of slow-waves**.

Context, methodology, results and discussions will be detailed in the main text. Published works related to the studies are consultable online from the links embedded at the beginning of each chapter.

3 STUDY 1 - SLEEP LEARNING OF SEMANTIC ASSOCIATIONS

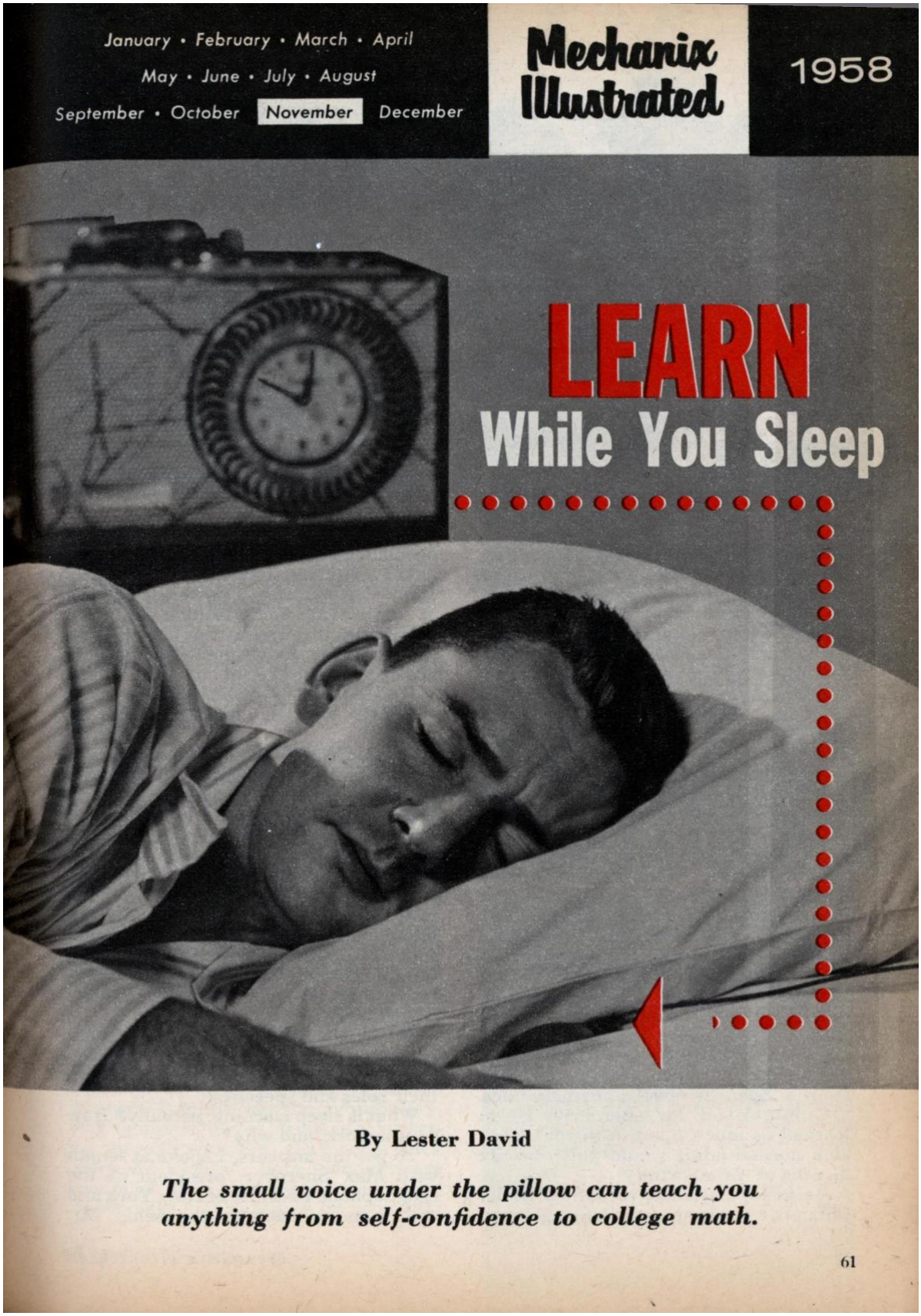
Hypothesis:

Semantic associations can be learned during light NREM sleep and REM sleep (**study 1**)

Related work:

Representation of retrieval confidence by single neurons in the human medial temporal lobe (3rd author, 2015, Nature Neuroscience)

Neural correlates of the formation of implicit semantic associations during NREM sleep (1st author, in preparation)



Cover of the Mechanix Illustrated illustrating the promises of sleep learning

3.1 Introduction

3.1.1 Is sleep learning real?

The benefits of sleep for second language consolidation is established (Fenn et al., 2003; Gais et al., 2006). Novel insights into its mechanisms have been recently obtained using the target memory reactivation technique (Schreiner & Rasch, 2017). Associations are first learned during wakefulness, e.g. between a word and its translation. Part of the association, e.g., the word, is then replayed during sleep. After awakening, this procedure boosts memory retrieval of the association, e.g., the meaning of the word (Schreiner & Rasch, 2015). **It was nevertheless demonstrated in mice that reactivations of memory traces can be also used to create new associations during sleep** (de Lavilléon et al., 2015). Similarly, we hypothesized that mechanisms linked to memory consolidation might be hijacked to form new semantic associations during sleep.

Compared to the consolidation of memories, acquiring entirely new linguistic associations during sleep is challenging (Peigneux et al., 2001). However, encoding of verbal information during sleep has been consistently demonstrated in the last few years (Ruch et al., 2014; Andrillon & Kouider, 2016). **Associative learning during sleep was also demonstrated for simple sensory stimuli** (Arzi et al., 2012; Arzi et al., 2014) **and recently extended to verbal associations** (Züst et al., 2019). Here, we investigate whether the meaning of words from an unknown language, Japanese, can be taught to naïve participants during sleep.

To do so, we played simultaneously a Japanese word and a corresponding sound (e.g., "*inu*" for dog and the barking sound of a dog "woof") during late-night sleep that is enriched in light NREM and REM sleep (Iber et al. (2007). Associative memory for verbal or any high-level information during these sleep stages has not been tested yet. Additionally, we used an identification task (e.g., "does this word correspond to a dog or a cat?") to test semantic memory rather than relying on a categorization task (e.g., "is the size of item bigger or smaller than a shoebox?") (Züst et al., 2019; Figure 11). We reasoned that this procedure tested more directly the semantic identity of a memory item rather than one of its associated property (e.g., its size). **To further demonstrate that the semantic identity was retrieved rather than a mere sensory memory, we used a cross-modal memory test where participants had to decide between two pictures which one of them corresponded to the Japanese word**. Finally, we asked to participants to report their confidence after each memory decision to investigate whether the memory was implicit or explicit.

	Low-level	**High-level**
Perceptual learning	(Andrillon et al., 2017)	(Andrillon & Kouider, 2016 ; Ruch et al., 2014)
Associative learning	(Arzi et al., 2014 ; Arzi et al., 2012 ; Ikeda & Morotomi, 1996)	(Züst et al., 2019)

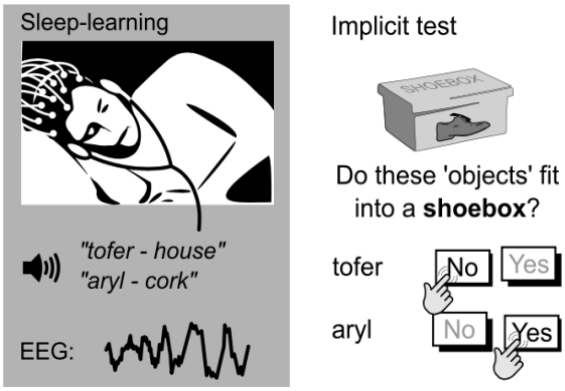


Figure 11 **State-of-the art of sleep learning in adults**. The left panel describes how studies converged recently to demonstrate the possibility of associative learning for high level sensory information during sleep. The right panel describes the paradigm designed by Züst and colleagues to demonstrate the acquisition of semantic information for newly encoded words during sleep. From Züst et al., 2019.

3.1.2 The nature of sleep learning

The distinction between implicit and explicit memory consists in being able to consciously access an information stored in memory (Tulving, 1987). **The two types of memory are supported by different cerebral systems** (Graf & Schacter, 1985; Gabrieli et al., 1995; Rugg et al., 1998). While memory acquisition during sleep has been considered implicit, studies have rarely directly tested this assumption (e.g., Wood et al., 1992; Züst et al., 2019; see Andrillon & Kouider, 2016 for an exception). To distinguish between conscious and unconscious memory traces, confidence scores can be collected from participants as conscious decisions typically yield higher confidence scores than unconscious ones (Yeung & Summerfield, 2012).

As an undergraduate, I took part to a study showing that subjective confidence at memory retrieval was encoded at the neuronal level in the human temporal median lobe, a system supporting explicit memory (Rutishauser et al., 2015). Yet, two separate processes were identified as contributing to confidence: one is related to the strength of the memory trace and the other one is related to the awareness of the memory trace (Chua et al., 2006). Confidence scores alone do not allow to disentangle cases where a memory trace is strong and retrieved implicitly from cases where the memory trace is weak and retrieved explicitly (as discussed in the context of visual masking by Kouider & Dehaene, 2007). **Yet, dissociations between first-order responses, i.e. memory performance (correct vs incorrect), and second-order response, i.e. confidence score, allows to infer that memories are retrieved implicitly** (Andrillon & Kouider, 2016).

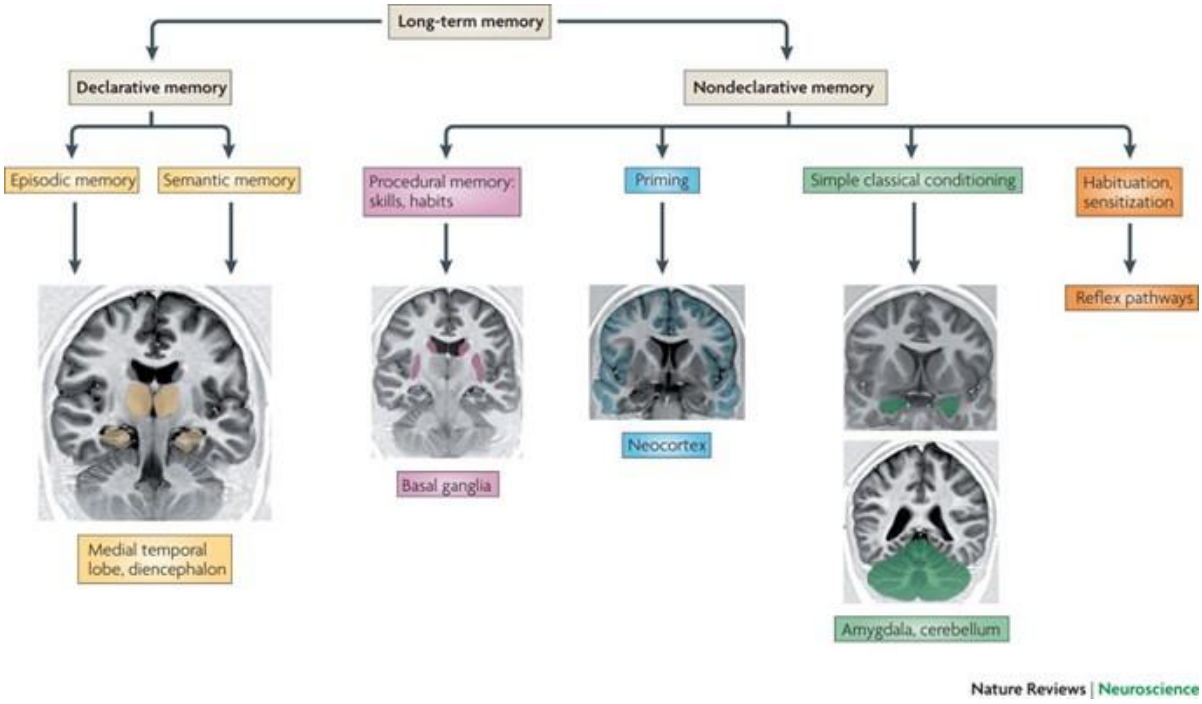


Figure 12 **Two memory systems.** Semantic memory, which is the memory of facts and general knowledge, is classically considered as a form of explicit, or declarative, memory. It is distinguished from implicit, or nondeclarative, memory. From (Henke, 2010)

While it is uncontroversial that semantic memory can be retrieved implicitly (Dehaene et al., 1998), whether it can be acquired unconsciously is disputed (Henke, 2010). Sensory conditioning is considered as a form of implicit memory and has been observed during sleep (Arzi et al., 2012; Arzi et al., 2014; Figure 12). Memory of higher-level associations such as linguistic word pairs is classically considered to rely on semantic memory which is considered as a form of explicit memory (Squire & Dede, 2015; Figure 12). **Conversely, Henke proposed that any associations, even for high-level information, can be formed unconsciously if they were repeatedly presented in the same format** (Henke, 2010). To test these hypotheses, paradigms probing unconscious learning mostly relied on modifying the conscious access to the information to memorize, e.g. through reducing the stimulus exposure below subliminal threshold (Kouider & Dehaene, 2007). Yet, an alternative approach is to present stimuli in a different state of consciousness. NREM sleep and REM sleep have been distinguished as consisting in two different conscious states (Hobson & Pace-Schott, 2002). Thus, different sets of stimuli will be delivered specifically in NREM or REM sleep in our study to investigate how associative memory acquisition for semantic information differs across conscious states.

3.1.3 Neural processes of sleep learning

Sleep learning experiments have demonstrated that memory formation crucially depends on sleep stages. Previous results associated light NREM sleep and REM with the promotion of sleep learning while deep sleep was associated with memory suppression (Andrillon et al., 2017). **Thus, we hypothesized that our effects would be optimized in restricting our experiment to the second part of the night that is enriched in light NREM and REM sleep**. Moreover, transfer of learning to wakefulness was higher for associations learned during light NREM sleep as compared to REM sleep (Arzi et al., 2012; Arzi et al., 2014). We thus predict that a higher memory retrieval will be obtained for items heard during light NREM sleep as compared to REM sleep.

Züst and colleagues demonstrated that new semantic associations could be encoded during deep NREM sleep but this effect crucially depended on slow wave activity (Züst et al., 2019; Figure 13). They presented word pairs separated by 1075ms to coincide with the slow wave rhythm (around 1 Hz). Presenting sound stimulation at a slow wave rhythm using a closed-loop procedure was found to boost slow wave activity and memory processes such as memory consolidation (Ngo et al., 2013; Papalambros et al., 2017). Conversely, presenting stimuli separated by half of a slow wave period, i.e. around 0.5s, disrupt slow waves and processes of memory consolidation (Ngo et al., 2013; Schreiner et al., 2015; Farthouat et al., 2017). In our study, Japanese words were repeated twice during sleep and separated by about 1090ms to foster sensory encoding and the entrainment of brain activity at a slow-wave rhythm during NREM sleep.

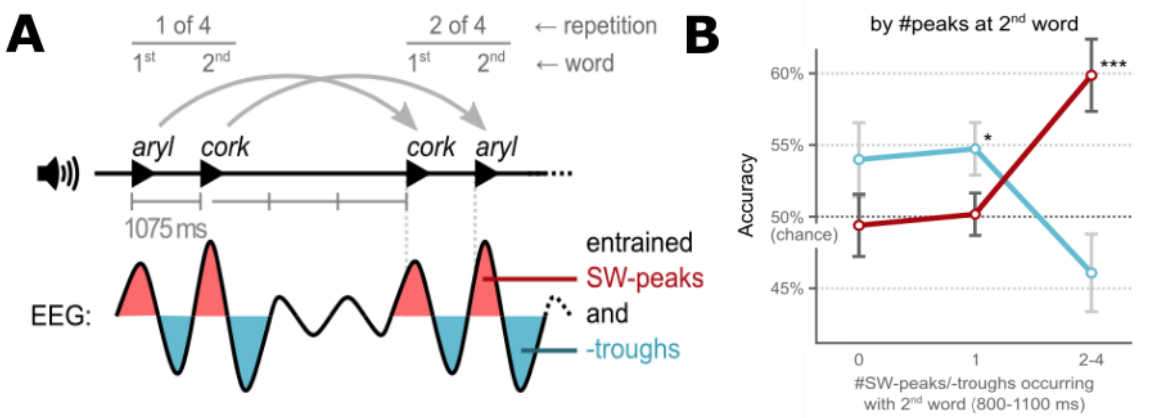


Figure 13 **Memory encoding of the meaning of pseudo-words depending on the presence of slow-waves peaks**. (**A**) Stimulation followed the slow wave rhythm occuring during slow-wave sleep. Additionally, order of presentation within word pairs were alternated across trials.
(**B**) Learning was mainly driven by the presence of slow wave peaks after the second presentation. From (Züst et al., 2019)

Brain entrainment at a slow-wave frequency also modulated learning for sensory conditioning during light NREM sleep (Canales-Johnson et al., 2020). **Neural dynamics of associative learning for higher level linguistic associations during light NREM sleep has not been investigated yet**. Canales-Johnson and colleagues furthermore investigated how brain responses evolved throughout the sleep learning process (Canales-Johnson et al., 2020). They analyzed neural responses to stimulations at the beginning and the end of sleep learning process. Thus, our last aim is to compare the neural responses across early and late sleep trials to track the sleep learning process and associated neural correlates of memory formation.

3.2 Methods

3.2.1 Stimuli

Japanese language was chosen because of the relative simplicity of its phototactic structure, its phonology close to French, and its wide distance from French vocabulary. **48 words from three categories were chosen (animals, natural elements, body parts or bodily actions)** (Table 6). Auditory versions of Japanese words were generated using a licensed-free online text-to-speech software (https://ttsmp3.com) and matched in intensity by normalizing by the root mean square.

Table 6 **List of the 48 Japanese word used for the experiment**. The English translation of Japanese word is indicated in parenthesis.

Tokei (clock)	**Mendori (chicken)**	**Jishin (earthquake)**
Ressha (train)	**Hitsuji (sheep)**	**Awa (bubble)**
Hikōki (airplane)	**Semi (grasshopper)**	**Yuki (snow)**
Jitensha (bike)	**Kamo (duck)**	**Denki (electricity)**
Kuruma (car)	**Hachi (bee)**	**Kesshō (crystal)**
Tsūka (coins)	**Kaeru (frog)**	**Kiji (cloth)**
Benjo (toilets)	**Uma (horse)**	**Kuchi (mouth)**
Hōki (broom)	**Hato (pigeon)**	**Shin (heart)**
Kane (bell)	**Iruka (dolphin)**	**Akanbou (baby)**
Inryou (drink)	**Karasu (crow)**	**Obake (ghost)**
Hasami (scissors)	**Shishi (lion)**	**Nodo (throat)**
Kage (keys)	**Okami (wolf)**	**Yubi (finger)**
Tobira (door)	**Nami (wave)**	**Shiga (teeth)**
kisen (cork)	**Hyōzan (ice)**	**Tenshi (angel)**
Hon (book)	**Taki (waterfall)**	**Suimin (sleep)**
Sosa (photocopy)	**Kaze (wind)**	**Warai (laugh)**
Hata (flag)	**Mori (forest)**	**Hana (nose)**
Inu (dog)	**Ame (rain)**	**utau (sing)**
Ushi (cow)	**Raiu (storm)**	**Nomu (drink)**
Tori (bird)	**Kasai (fire)**	**Naku (cry)**
Buta (pig)	**Hoshi (star)**	**Taberu (eat)**
Fukurō (owl)	**Shītoī (leaf)**	**Hara (belly)**

Japanese words were paired with characteristic sounds (e.g., a barking dog for "*inu*"). Sounds were extracted from licensed-free online audio banks (http://eng.universal-soundbank.com; https://www.freesoundeffects.com) and matched in length using the VSOLA algorithm (duration = 2.58). Sound intensity across auditory stimuli were normalized by their root mean square. Corresponding images for Japanese words were selected from online databases and were matched in size. **This procedure resulted in 48 associations between a Japanese word (e.g., *inu*), a corresponding sound (e.g., "woof") and a corresponding image (e.g., the image of a dog).**

For each participant, the 48 items were randomly assigned to 3 lists of 16 items, resulting in a NREM, a REM and a Control list which items were not presented during sleep. **For the two other lists, Japanese words were played simultaneously with their corresponding sounds during sleep.** Japanese words were repeated twice to enhance sensory and memory encoding (first word onset after sound onset=0.5s, second word onset = 1.59±0.10, mean±SD across stimuli).

3.2.2 Protocol

Twenty-five French-native speakers were recruited for this study based on online questionnaires. **Participants without repeated exposure to Japanese, Chinese or Korean were included**. They had no history of hearing nor sleep disorders. To ensure normal sleep schedule during the week before the study, they were monitored by actimetry (Fitbit Charge HR) and filled a sleep diary. They were refrained from consuming stimulants (e.g., caffeine) the day of the experiment. Two participants were excluded from our analyses due to their difficulties to fall asleep and an additional one due to technical issues, resulting in twenty-two participants (age: 23,7, min: 20, max: 29, 15 females).

Participants started the experiment around 3am. They were equipped with a 64-channel EEG gel-net (EGI system, Electrical Geodesic Inc.) and chin EMG. Participants started with a learning phase during which images and their corresponding sounds were presented four times in randomized order (e.g., a picture of a dog and the sound "*woof*") (Figure 14). Then, participants were allowed to fall asleep while sounds (e.g., "*woof*") from the three lists were continuously played separated by a 4s to 6s uniformly distributed random jitter. Volume was adjusted according to participants' preference and set around 50dB in line with previous experiments (Strauss et al., 2015; Andrillon et al., 2017). **Whenever participants entered NREM or REM sleep, sleep items** (e.g., "woof" with '*inu*' repeated twice) from the corresponding list were played.

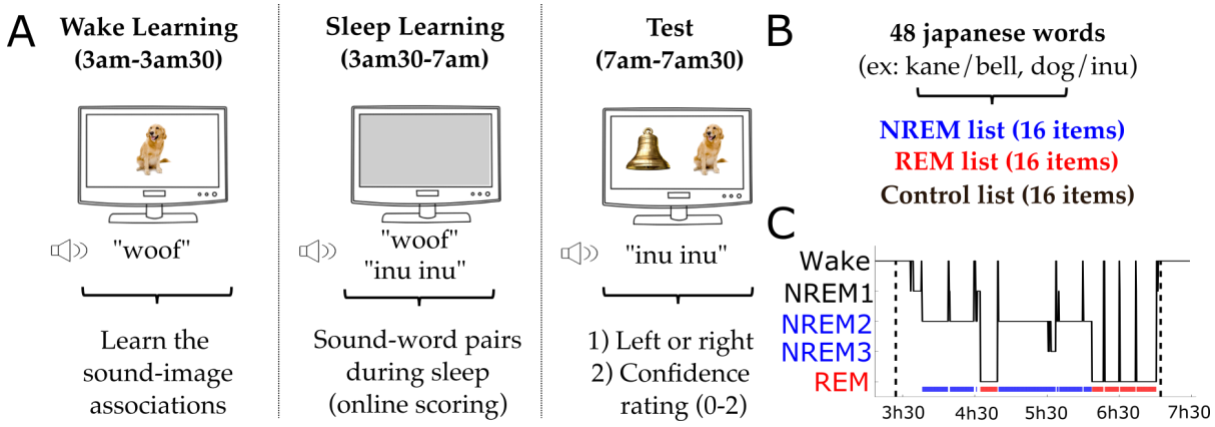


Figure 14 **Experimental protocol for learning Japanese stimuli during sleep**. Participants were invited to the sleep lab the evening prior to the experiment (panel A for the course of the experiment). They were awakened at 3am for a wake learning phase (30 minutes). During this phase, forty-eight sound-image pairs were presented four times to allow participants to learn the associations between a sound, e.g. "woof", and an image, e.g. a dog. Then participants were allowed to fall asleep while the sounds ("woof") were continuously presented. During the sleep learning phase, sleep items from the corresponding lists, i.e. respectively NREM and REM lists (see panel B), were played only if participants were scored online by a trained scorer (M.K) as either being in NREM (NREM2 and NREM3) or REM sleep (panel C for an example of a sleep hypnogram). Sleep trials consisted in Japanese translations (e.g. "*inu*") repeated twice on top of their corresponding sounds (here "woof"). At 7am, participants were awakened for the test phase. The memory test consisted in a two-alternative forced choice (2AFC) task. Participants heard a Japanese word (e.g. "*inu*") repeated twice to facilitate recognition and had to choose between 2 images, one being the corresponding image and the other belonging to another association. The two images belonged to the same list (i.e., NREM, REM, or Control list). Participants had then to provide their confidence in their memory response on three-level scale (0: null, 1: low or 2: high confidence).

Then, participants woke up between 7am and 7am15 and started the test phase (Figure 14). **Pictures were randomly paired with a picture from another item from the same list, resulting in 16 pairs for each list**. Each picture appeared once as the correct response and once as the wrong response during the test. Side (left or right) of the correct response and apparition of the same item as correct or incorrect was counterbalanced within lists. The order of apparition of items across all lists was randomly shuffled. Participants could correct their initial response before providing their confidence score in order to avoid mistakes in button press and foster adequate confidence judgments in relation to their memory choice.

3.2.3 Analysis

EEG signals were amplified (NetAmp 300), referenced online to Cz and sampled at 500 Hz. EEG and EOG signals were re-referenced to mastoids and bandpass filtered between 0.1 and 30 Hz (two-pass Butterworth filter, 5th order). EMG signal were obtained with a local derivation and band-passed between 80 and 160 Hz (two-pass Butterworth filter, 5th order). EEG recordings and audio stimuli were synchronized using a third audio channel. Defective channels were interpolated using neighboring electrodes for offline analyses. Sleep stages were scored online by a trained scorer (M.K.) following established guidelines (Iber, 2007). **Sleep stages were additionally scored offline on 20-s long windows by trained scorers (M.K. and D.L.).** Micro arousals were carefully noted. Table 7 summarizes the number of stimuli presented in each phase across subjects and Table 8 the sleep statistics for the sleep learning phase.

Table 7 **Summary of number of repetitions of items for NREM and REM lists during the sleep learning phase**. The number of repetition of items varied across participants due to difference in sleep patterns and differences in the efficiency of the online sleep scoring across sleep stages. Sleep scoring was performed online (M.K.) and offline by two trained scorers (M.K and D.L.). The online scoring efficiency was computed by dividing the amount of trials of a given list that were played in the correct sleep phase over the total number of trials that were played during the sleep learning phase.

Number of repetitions	**NREM list (16 items)**	**REM list (16 items)**
in NREM sleep (N2 and N3)	40±2.6	1.8±0.38
in REM sleep	0.61±0.21	13±1.2
in Wakefulness (Wakefulness and N1)	0.45±0.12	0.23±0.06
Online scoring efficiency	97±0.5%	85±3.6%

Table 8 **Sleep statistics during the sleep learning phase**. Sleep onset latency was defined as the first apparition of stage NREM2 since the beginning of the sleep phase. Sleep efficiency was calculated as the percentage of time spent in N1, N2, N3 or REM sleep during the sleep phase.

	Sleep duration (min)	**Duration of light NREM sleep (min)**	**Duration of deep NREM sleep (min)**	**Duration of REM sleep (min)**	**Sleep latency (min)**	**Sleep efficiency (%)**
Mean±SD	165±6.5	102±5.7	23±4.7	39±3.5	26±3.9	81±1.8

EEG recordings were then resampled at 100 Hz for data analysis. EEG responses from -0.5 to 4.5 s around stimulus onset of each trial were selected. Brain responses were baseline corrected ([-0.2, 0]s). The difference between the maximal amplitude and the minimal amplitude (maximal difference) for each trial and each electrode was computed. The mean and standard deviations (SD) of the maximal differences across trials for each electrode was computed. Trials with at least one electrode deviating for more than 3 SD above the mean were rejected to avoid artifactual contamination (5.0%, CI=[4.1, 6.1]). This resulted in conserving 1689 trials (CI=[1619, 1758]). Among these trials, only trials that belonged to NREM sleep both online and offline were kept for further analysis, resulting in 625 trials (CI=[540, 711]) per participant. **Following previous study, potentials for channels over a frontal cluster of electrodes (Fz, F1, F2, F3, F4, FPz, FP1, FP2, FP3, FP4) were averaged across trials of the same condition** (Züst et al., 2019). Time-courses of the brain responses were averaged across participants and smoothed for visualization purpose only, using a 500-ms wide Gaussian kernel. Statistical tests were performed on brain responses before smoothing. Post-hoc analyses were averaged across participants.

Memory performance were compared to chance-level (50%) using parametric statistics (Student's T-test). Confidence scores and neural amplitudes were compared between correct and error responses using parametric tests (paired Student's T-test). Tests were corrected for multiple comparisons using Bonferroni correction. Bayesian statistics were computed using the bayesFactor toolbox in Matlab to support evidence for null results (i.e., a Bayes Factor above 3) (Krekelberg, 2019). **To investigate the effect of lists on performance score, repeated-measure ANOVA were performed with participant as a random factor.** To investigate the interaction of lists and confidence on memory performance, linear mixed models were computed using the Matlab functions fitlme with participants as a random effect. All variables of interest were defined as categorical values and the Control list was fixed as reference. To establish whether repetitions of trials could better predict memory performance than sleep stages, we used a chi-square (χ^2) test. A model with number of repetition and sleep stages as fixed effects and participant as a random effect was compared to the same model without the number of repetitions of stimuli as fixed effect. When analyzing the time-course of brain responses, non-parametric cluster permutation statistics were computed to control for multiple comparisons. Clusters were defined as consecutive time-points for which parametric tests reached a specific threshold (α=0.05). For each cluster, the sum of t-values was compared to the maximum cluster statistics obtained after random permutation of the conditions considered (N = 1000 permutations). We computed a Monte-Carlo P-value (referred as $P_{cluster}$) and the sum of t-values of clusters with $P_{cluster}<0.05$ were reported.

3.3 Results

3.3.1 Behavioural results

We first investigated whether participants acquired the meaning of the words presented during sleep. We observed that memory performance depended on the list tested (repeated measure ANOVA, $F(2,21)=4.66$, $p<0.05$; Figure 16A). **Memory was above chance (50%) for words from the NREM list** (59%, CI=[52, 66], $t(21)=2.7$, $p<0.05$, corrected for multiple comparison; Figure 15A). Comparatively, memory was not different from chance for words from the REM list (53%, CI=[48,58], $t(21) =1.32$, $p>0.05$, corrected for multiple comparison; Figure 15A). Memory for words that were not presented during sleep, i.e. the Control list, was also not above chance level, confirming that participants did not know Japanese (45%, CI=[38, 53] ; $t(21)=-1.31$, $p>0.05$, corrected for multiple comparison; Bayes Factor : 10.3, Figure 15A). Finally, we checked whether excluding the items from the NREM list that were played during brief awakening periods was affecting our results (3.4 items, CI=[2.0, 4.8], see Table 7). We confirmed that memory performance was higher than chance for the NREM sleep list even after removing these items (58%, CI=[50, 68] ; one-tailed Student's t-test against chance level (50%), $t(20) = 2.0$, $p=0.027$). These results confirm that the meaning of Japanese words was acquired during NREM sleep.

We then studied whether the memory during NREM sleep was implicit or explicit. If memory during NREM sleep was explicit, we hypothesized that the confidence scores for NREM list would be high and higher than for the Control list. Additionally, higher confidence scores are expected for correct memory choices (correct) as compared to incorrect ones (error). First, we found that confidence was scored as random or low for the NREM list (0.67, CI=[0.52,0.81] ; Figure 15B), indicating that confidence was weak (Figure 16B). Second, we found no difference in confidence for the NREM list as compared to the Control list (-0.03, CI=[-0.1, 0.05]; $t(21)=-0.78$, $p>0.05$; Bayes Factor : 7.7; Figure 15B). **Third, we found no difference in confidence between correct and error trials** (0.003, CI=[-0.1, 0.1], $t(21)=-0.78$, $p=0.48$; Bayes Factor : 4.3; Figure 15B).

A limitation of such analysis relying on negative evidence is that participants might not correctly use the confidence scale. To investigate this hypothesis, we relied on mixed-model analyses. Memory performance predicted confidence score differently for the NREM list and the Control list, which was not observed when comparing the REM list and the Control list (correct vs incorrect x Control vs NREM, $t(150)=-2.43$, $p<0.05$; correct vs incorrect x Control vs

NREM, t(150)=-1.23, p>0.05, corrected for multiple comparison). This was not due to an unbalanced number of trials across lists (Figure 15C). We then found that confidence predicted memory performance for the Control list (t(51)=3.20, p<0.01) but not for the NREM list (t(48)=-0.46, p>0.05) (Figure 15D). **Overall, this excludes the hypotheses that participants did not use the scale and that memory in NREM sleep is tied to a few high confidence items.**

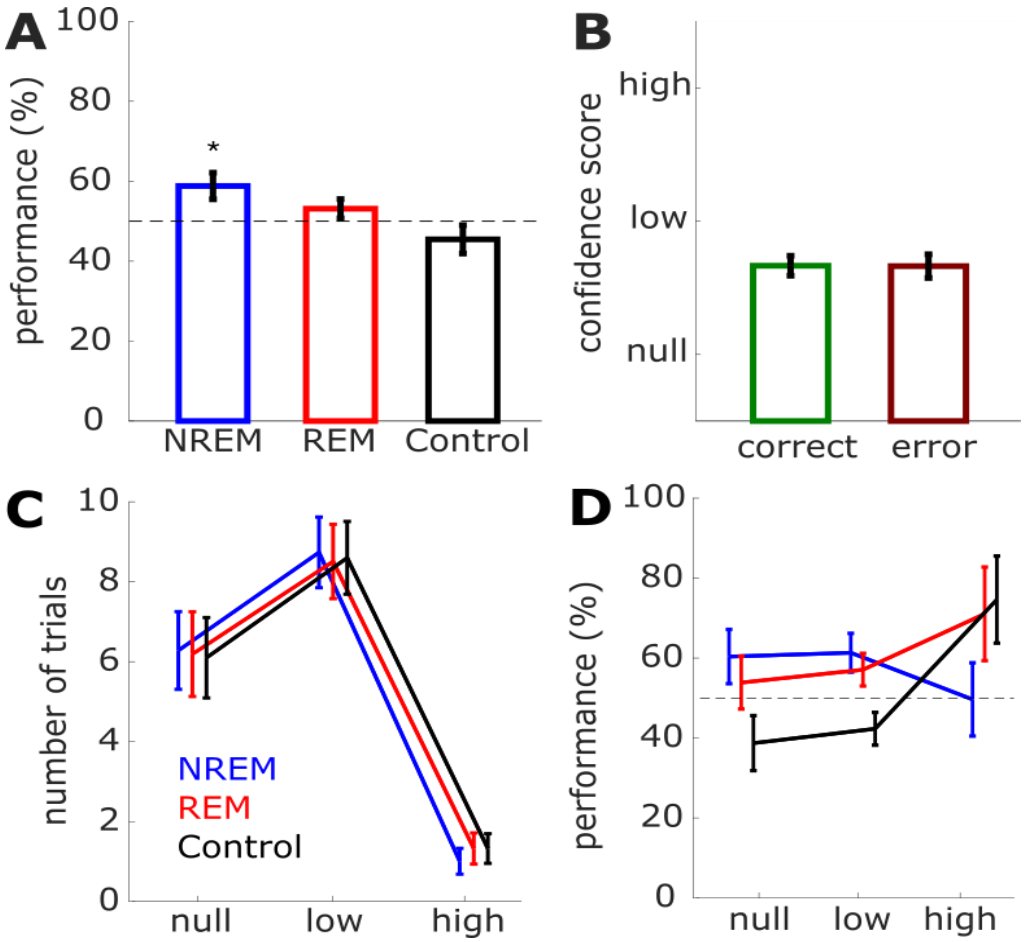


Figure 15 **Evidence for implicit memory for semantic associations presented during NREM sleep.** (**A**) Memory performance across NREM, REM and Control list. Student's T-test against chance level (50%, dotted line) were computed for each list and corrected for multiple comparisons. Mean and standard error of the mean (SEM) are represented respectively with bar plots and solid lines for NREM (blue), REM (red) and Control (black) lists.

(**B**) Confidence score on a 3-level scale (null, low, high) for memory response of the NREM list. Statistical tests reveal no difference between trials that were successfully identified (correct) and those associated with a mistake (error). Mean and SEM are represented

(**C,D**). Number of trials (C) and performance (D) was computed for each confidence category (null, low and high) and each list (NREM, REM and Control) separately. Mean and SEM are represented respectively for NREM (blue), REM (red) and Control (black) lists.

3.3.2 Differential neural response during sleep predict memory performance

To understand the factors that determine associative memory for words during NREM sleep, we investigated whether brain responses during word presentations during sleep successfully predicted memory retrieval. To do so, we contrasted brain responses for stimuli that were later correctly identified during the memory test (correct) and those associated with a mistake (error). Brain potentials were averaged over a frontal region-of-interest where slow waves have the strongest amplitude and where memory effects have been reported in previous literature (Massimini et al., 2004; Züst et al., 2019). For both correct and error trials, we obtained as expected a modulation of the brain responses to our stimuli occurring after the first and second word presentation (Figure 17A, correct : [0.94, 1.67]s, $t(21)=-353.7$, $P_{cluster}<0.01$ and [2.09, 2.89]s, $t(21)=-353.7$, $P_{cluster}<0.05$; error : [0.90, 1.68]s, $t(21)=-414.9$, $P_{cluster}<0.001$ and [2.14, 2.70]s, $t(21)=-192.7$, $P_{cluster}<0.05$). **We found additionally a significant difference between correct and error trials emerging after the end of stimulation** ([3.36, 3.93]s, $t(21)=-120.1$, $P_{cluster}<0.05$).

We hypothesized that this difference resulted from the entrainment of neural oscillations at a slow-wave (SW) rhythm (Bastien & Campbell, 1992; Halász, 2016). We thus investigated in more details the amplitude of brain responses over negative half-periods (troughs) corresponding to the human SW activity (0.85 Hz; grey bars, Figure 16A). Post-hoc tests confirmed that amplitudes differed significantly from baseline for both correct and error trials at the 1st and 2nd SW troughs ($p<0.05$, corrected for multiple comparisons; Figure 16B). Brain topography of these responses indicated that amplitudes were maximal over frontal electrodes (Figure 16B). Post-hoc results did not reveal any difference between correct and error trials for the 1st and 2nd. SW trough ($p>0.05$ for the 1st and 2nd SW trough). **Yet, for the 3rd SW trough, post-hoc comparisons confirmed a lower amplitude for correct trials compared to error trials** (-3.22 μV, CI=[-6.3, -0.2], $t(21)=-2.2$, $p<0.05$; Figure 16B).

To ensure that these results were not valid only for trials in deep NREM where slow-wave activity is stronger than in light NREM sleep, we conducted the same analysis restricting trials to light NREM sleep (484 trials per participants, CI=[401, 568], see Table 7). We showed that the same results hold in light NREM sleep with differences between correct and error trials spanning over the whole 3rd SW ([2.76, 3.89]s, $t(21)=-248.7$, $P_{cluster}=0.017$; Figure 16C). **Post-hoc tests confirmed that our previously described effects are also verified for light NREM sleep** (-4.8 μV, CI=[-9.3, -3.8], $t(21)=-2.3$, $p<0.05$; Figure 16D).

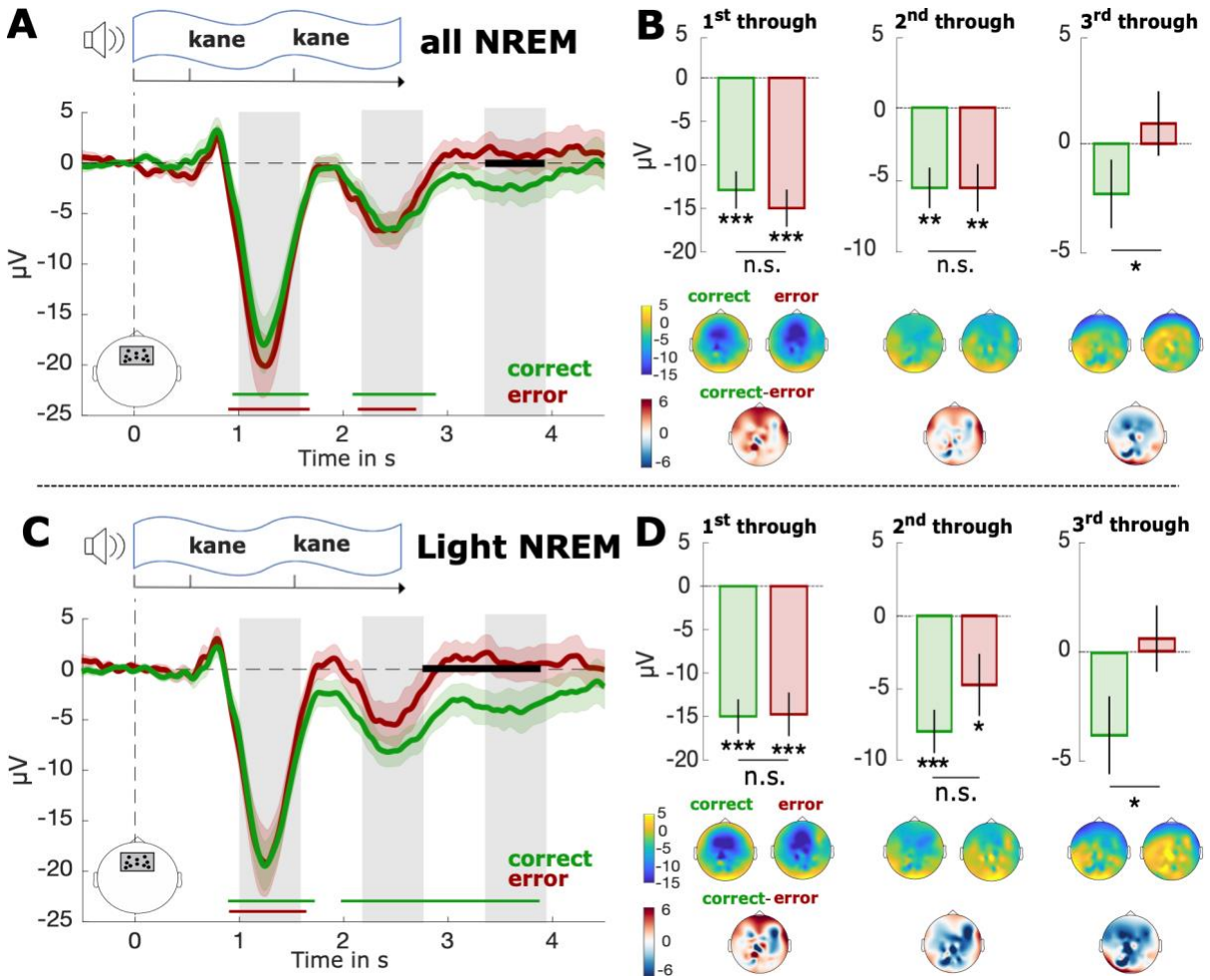


Figure 16 **Differential entrainment of frontal neural responses at a slow-wave frequency to stimulus presentation for correctly and incorrectly identified items during NREM sleep.** (**A**) Neural responses were computed over a frontal cluster of electrodes depicted in the lower left panel. Time-course of the stimulus presentation was indicated in a top panel. Mean and SEM are represented respectively with solid lines and shaded areas for the correct (green) and the error (red) trials. Green, red and black horizontal lines denote significant clusters of neural responses differing from baseline (0, dotted line) for respectively correct, error, and the difference between both conditions (P<0.05 after cluster correction, see *Methods*). Grey bars indicate time clusters corresponding to the troughs of a rhythm at 0.85 Hz.

(**B**) Neural responses were averaged for each trough and compared between correct (green) and error (red) trials. Mean and SEM are represented with bar plots and solid lines. Student's T-test against baseline (0, dotted line) was computed for correct and error trials and corrected for multiple comparisons. Paired Student's T-test were computed between correct and error trials (***: P<0.001, **: P<0.01, *: P<0.05). Topography of amplitudes were indicated in lower panels for correct, error and the difference between correct and error trials.

(**C-D**) Same as above for trials restricted on light NREM sleep

3.3.3 Dynamics of sleep learning

Finally, we investigated whether we could track the learning process over the course of the night. To do so, we split the sleep learning phase in two parts and compared brain responses for correct and error trials in the 1st and 2nd half of the sleep learning phase. For the 1st half of the sleep learning phase, we found a significant cluster with a higher response for correct compared to error trials that span over the 1st SW ([0.59, 1.48]s, t(21)=205.0, $P_{cluster}$ = 0.025; Figure 18A). **For the 2nd half of the sleep learning phase, two late clusters emerged with a lower response for correct as compared to error trials during the 3rd SW** ([3.16, 3.56]s, t(21)=-88.9, $P_{cluster}$<0.05, ([3.67, 4.05]s, t(21)=-90.0, $P_{cluster}$<0.05) (Figure 18B).

We then described each SW period separately. We investigated whether the difference between correct and error trials interacted with the course of learning when comparing the first and second half of sleep learning. **We found an interaction for 1st SW and the 2nd SW periods** (repeated measures ANOVA; 1st SW: F(1,21)=4.52, p<0.05, 2nd SW : F(1,21)=4.45, p<0.05; Figure 18 C, D). Post-hoc analyses revealed that for the 1st SW, brain differences between correct and error trials were restricted to the 1st half of trials, suggesting that early responses reflect differences relative to the initial encoding of stimuli (4.9 μV, CI=[1.1,8.7], t(21)=2.68, p<0.05, corrected for multiple comparison; Figure 18C). For the 2nd SW, the difference between the 1st and 2nd half consisted in an inversion of the pattern of response, resulting in brain potentials lower than baseline for error trials in the 1st half and for correct trials in the 2nd half (1st half error : -5.7 μV, CI=[-10.3,-1.1]; t(21)= -2.56, p<0.05; 2nd half correct : 5.7 μV, CI=[-8.5,-2.8]; t(21)= 4.19, p<0.01, corrected for multiple comparison; Figure 18 C, D). This suggests that the entrainment of the brain at a slow-wave frequency emerged during sleep learning.

Despite no interaction was found at the 3rd SW (repeated measures ANOVA; F(1,21)=1.06, p<0.05), post-hoc tests showed lower responses for correct trials compared to error trials only the 2nd half of the night (-4.2 μV, CI=[-7.7,-0.7] ; t(21)=-2.46, p<0.05, corrected for multiple comparison; Figure 18E). **Overall, these results demonstrate that neural responses predicting correct responses evolve over the course of learning during sleep.**

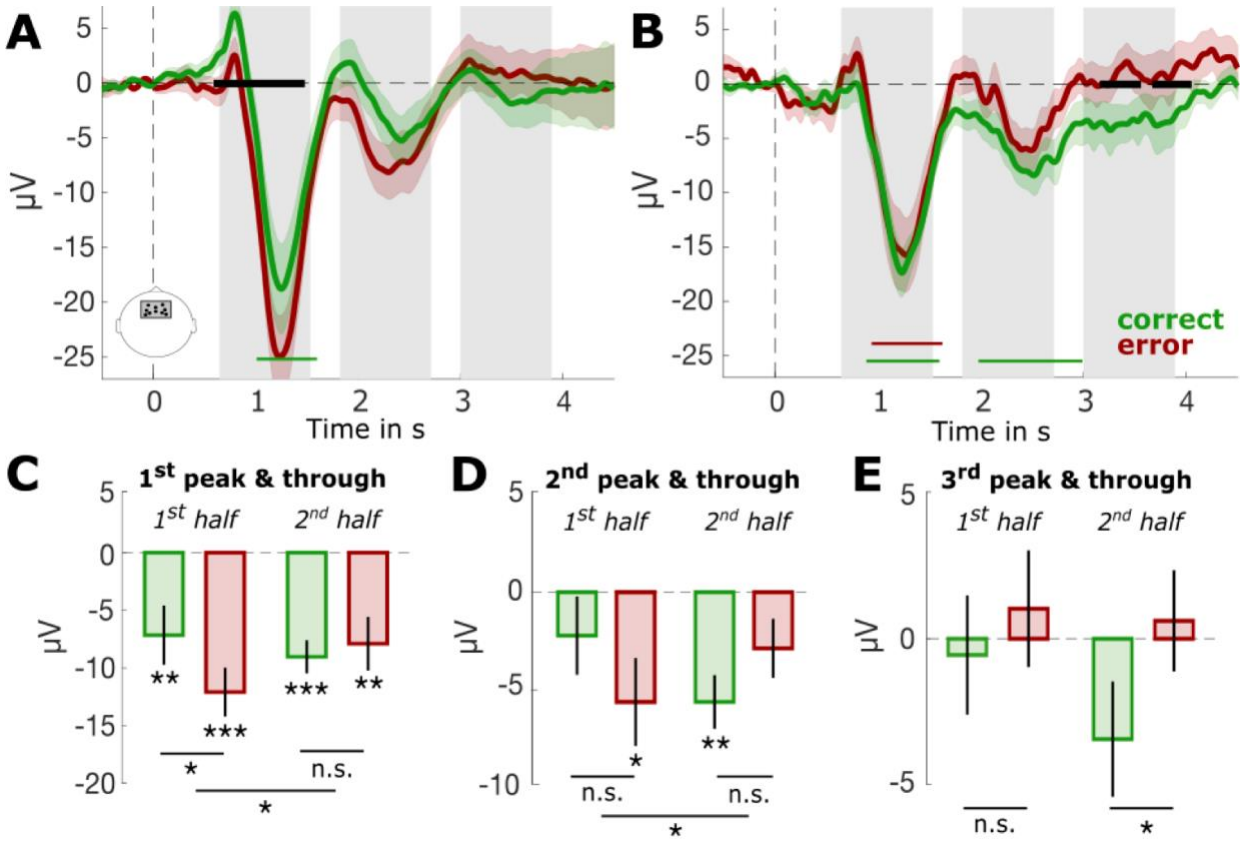


Figure 17 **Differential entrainment of frontal neural responses by stimulus presentation for correctly and incorrectly identified items for the first half of trials and the second half of NREM trials.** (**A,B**) Neural responses were computed over a frontal cluster of electrodes depicted in the lower left side of panel A. Mean and SEM are represented respectively with solid lines and shaded areas for the correct (green) and the error (red) trials for the first (A) and second (**B**) half trials in NREM sleep. Green, red and black horizontal lines denote significant clusters of neural responses differing from baseline (0, dotted line) for respectively correct, error, and the difference between both conditions (P<0.05 after cluster correction, see *Methods*). Grey bars indicate time clusters corresponding to the troughs of a rhythm at 0.85 Hz.

(**C-E**). Neural responses for correct (green) and error (red) trials for the first and second half of trials were averaged and compared for the first (A), second (B) and third (C) peak and trough. Mean and SEM are represented respectively with bar plots and solid lines. Student's T-test against baseline (0, dotted line) was computed for correct and error trials and corrected for multiple comparisons. Paired Student's T-test were computed between correct and error trials for and corrected for multiple comparison. Interaction between trial type (correct vs error) and period of the night (first vs second half) for each peak and trough were computed with repeated measures ANOVA (***: P<0.001, **: P<0.01, *: P<0.05).

3.4 Discussion

3.4.1 Dynamics of sleep learning

Our results show that semantic associative learning for foreign words can be formed during NREM sleep and retrieved implicitly at awakening. Thus, our study provides further evidence showing that semantic associations can be acquired during NREM sleep. Furthermore, it extends previous results by studying light NREM rather than deep NREM sleep and using a novel paradigm relying on a cross-modal identification task. A first important remark is to stress that the amplitude of memory gain observed here for NREM sleep is small (around 60% as compared to chance-level of 50%). **This effect size is similar to previous results obtained for the learning of novel semantic associations during deep NREM sleep** (Züst et al., 2019).

We additionally show that memory retrieval is observed in light NREM sleep but not during REM sleep. This is in line with previous results showing that retrieval of associative learning formed during REM sleep is lower than during light NREM sleep (Arzi et al., 2012; Arzi et al., 2014; Figure 18). A first explanation could be that internal activity during REM sleep prevents the formation of memory of external stimuli. As dreams are more frequent during REM sleep, it has been proposed that dreaming activity gates the processing of external stimuli (Nir & Tononi, 2010; Andrillon & Kouider, 2020). Stimulations played in REM sleep represented yet only a quarter of our stimulus presentation. Thus, it might be alternatively that stimuli were not repeated enough to allow for the formation of semantic associations. The fact that the memory was implicit in light NREM sleep rather than explicit reinforces the hypothesis that repetition might be necessary for memory encoding. In this study, we could not differentiate the effect of repetition and sleep-stage specific effects. Thus, further experiments are needed to settle this question.

Even if REM sleep is not directly associated with memory formation, an interesting possibility remains that REM sleep could still benefit to NREM sleep learning. **Indeed, according to the sequential hypothesis, REM sleep would participate in reorganizing memory traces that have been consolidated during NREM sleep** (Giuditta et al., 1995). Accordingly, the presence of REM sleep has been shown to benefit the integration of new vocabulary into existing semantic networks (Batterink et al., 2017; Tamminen et al., 2017). Thus, it might be that REM sleep takes part to the memory formation of NREM items and contribute to the evolution of neural markers of sleep learning observed between the first and second half of sleep learning trials.

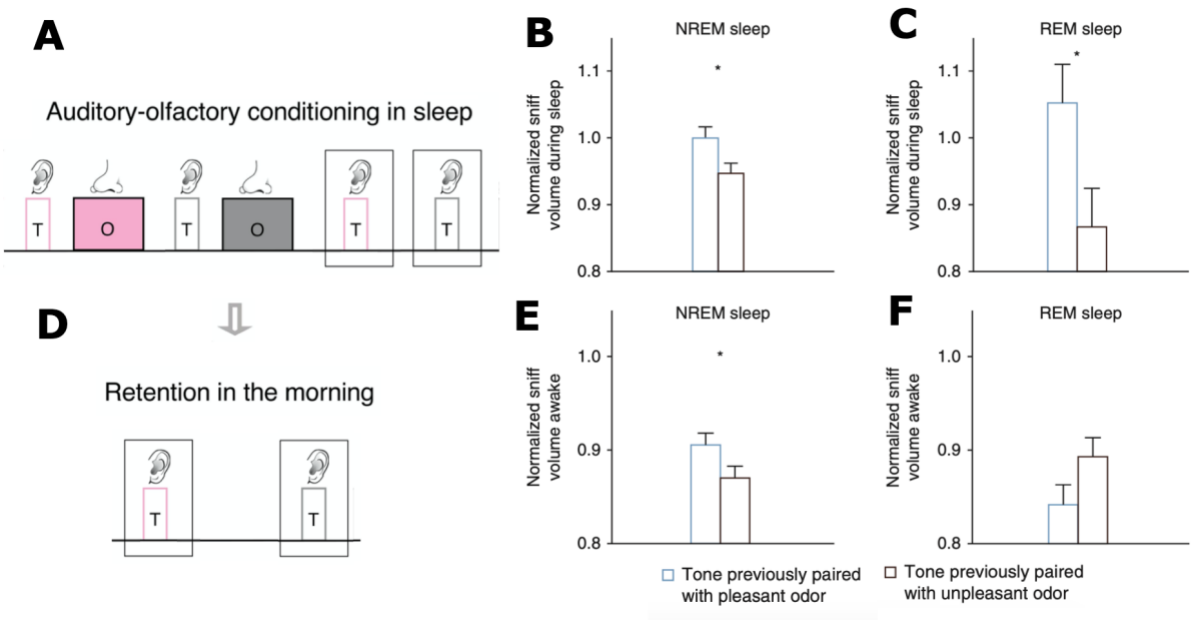


Figure 18 **Memory recall in an auditory–olfactory discriminatory learning paradigm.** (**A**) Auditory stimuli (1,200 Hz or 400 Hz) were reinforced with a pleasant (shampoo or deodorant, pink) or an unpleasant odor (rotten fish or carrion, grey). Additionally, non-reinforced trials (tone alone) were played during the sleep learning phase to test whether the presentation of sounds alone modified behavior during sleep. T, tone; O, Odor.

(**B,C**) Normalized sniff response across continuous repetitions of a tone alone previously paired during sleep with a pleasant odor (CSp, pink) or with unpleasant odor (CSu, grey) during the first five non-reinforced presentation of each CS during NREM sleep (B) or REM sleep (C)

(**D**) Only non-reinforced trials were played at awakening in the morning for pleasant (pink), or an unpleasant odor (grey). T, tone.

(**E,F**) Normalized sniff response during the retention session for NREM (E) and REM sleep (F) Statistical analysis was conducted using one-tailed *t* test. *, $P < 0.05$

From Arzi et al., 2012 and Canales-Johnson et al., 2020

3.4.2 The nature of sleep memory

We showed evidence that participants had poor confidence in their memory and were not more confident for items presented during NREM sleep as compared to items that were never presented (Control list). Finally, confidence ratings did not differ between correct and error trials. **These results suggest that memory is implicitly retrieved during the memory test.** Such absence of explicit memory for semantic associations during sleep is in line with previous literature (Ruch et al., 2014; Andrillon & Kouider, 2016; Züst et al., 2019).

To confirm that learning during wakefulness was qualitatively different from sleep learning, we performed a control task with new participants (n=12). The task structure was the same except the sleep learning phase was replaced by four repetitions of twenty-four auditory associations (e.g., Japanese translations with their corresponding sounds) played whilst being awake. The Control list was composed of twenty-four items that were not presented during this learning phase. Results show that performance for items played in wakefulness was high (88%, CI=[80, 97]; Student's t-test against baseline (50%), t(11)=10.1, p<0.001; Figure 19A) and was higher than items of the Control list (Student's t-test between the two conditions, t(11)=7.1, p<0.001; Figure 19A). Performance for items of the Control list was around chance level (52%, CI=[45, 59]; Student's t-test against baseline (50%), t(11)=0.68, p=0.51, Bayes Factor: 1.9; Figure 19A). Moreover, confidence was high for wake items (2.8, CI=[2.7, 2.9]), higher than for the control list (Student's t-test, t(11)=8.4, p<0.001), and higher for correct trials compared to error trials (repeated measures ANOVA; F(1,8)=10.91, p=0.01; post-hoc Student's t-test correct vs incorrect for the wake list,

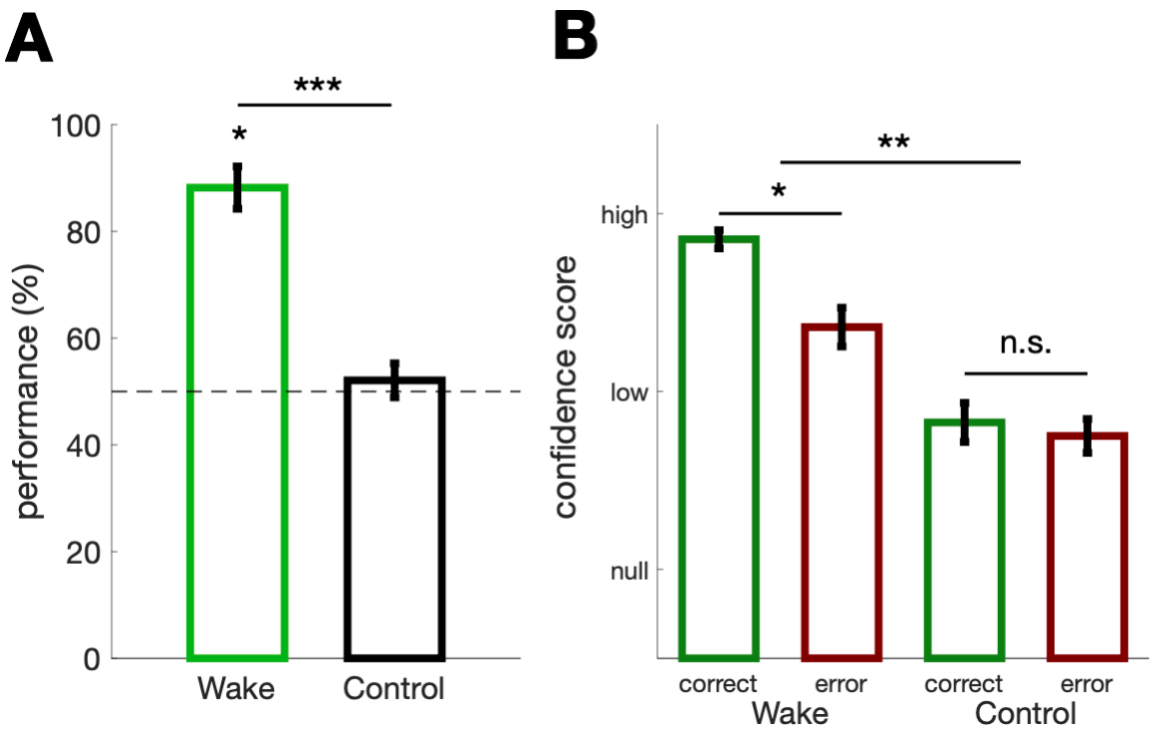


Figure 19 **Control experiment at wake (n=12).** (**A**) Memory performance for wake (24 items) and Control (24 items) list. This experiment followed the same structure as the sleep experiment, except the sleep learning phase was performed at wake and associations were repeated 4 times. (**B**) Confidence score for the wake and control lists. Interaction between memory response (correct vs. error) and list (wake vs. control) was tested with repeated-measure ANOVA. Differences across conditions were computed with paired Student's T-test (**, P<0.01; *<0.05, n.s., not significant).

t(8)=4.43, p=0.002) (Figure 19B). These results provide evidence for explicit memory in wakefulness despite relying on more items (24 against 16) and fewer repetitions (10 times less, 4 times during wakefulness in the wake control experiment vs. 40 during light NREM sleep in the sleep experiment). **This result shows that this paradigm triggers explicit memory effects when it is performed during wakefulness and thus further reinforces that retrieval of associations learned during sleep is implicit.**

A more detailed analysis of the use of the confidence scale in the sleep experiment revealed the presence of few items with high performance and high confidence in the control conditions (around 1 item per participants, Figure 15C). This suggests that a restricted number of items were already known by participants. This effect was yet absent in the NREM list and did not drive our effects, revealing that memory observed here was truly implicit. Yet, it might suggest that participants had previous exposure, at least for a word per list, with Japanese before. **This does not allow to exclude that memory traces for Japanese words could have been encoded during wakefulness and reactivated during our experiment.**

3.4.3 Neural markers of associative learning

Memory performance could be predicted from the brain activity evoked by stimulus presentation during sleep. Brain responses over a frontal cluster of electrodes reflected the entrainment of neural responses at a slow-wave frequency (0.85 Hz). **This result adds evidence that the entrainment of slow waves over the frontal brain region constitutes a marker of memory encoding during sleep** (0.85Hz here against 0.8Hz for Züst and colleagues; Figure 20). While we observed that a SW trough predicted memory performance, Züst and colleagues observed that memory performance correlated with an enhancement of slow-wave peaks. This difference can be explained by the different sleep phases targeted by both experiments. Slow waves are more frequent and more sustained in deep sleep, leading to more consistent SWA. Importantly, we showed that our results hold true when restricting our analyses on light NREM sleep. Yet, we lacked enough trials to test whether our results changed when focusing on deep NREM sleep.

We investigated furthermore the dynamics of the learning process. Our analysis revealed that, at the beginning of the learning process, frontal response right after the presentation of the first Japanese word is bigger for correct trials as compared to error trials. This could reflect a higher cortical reactivity to items that were successfully remembered in the initial encoding phase of the

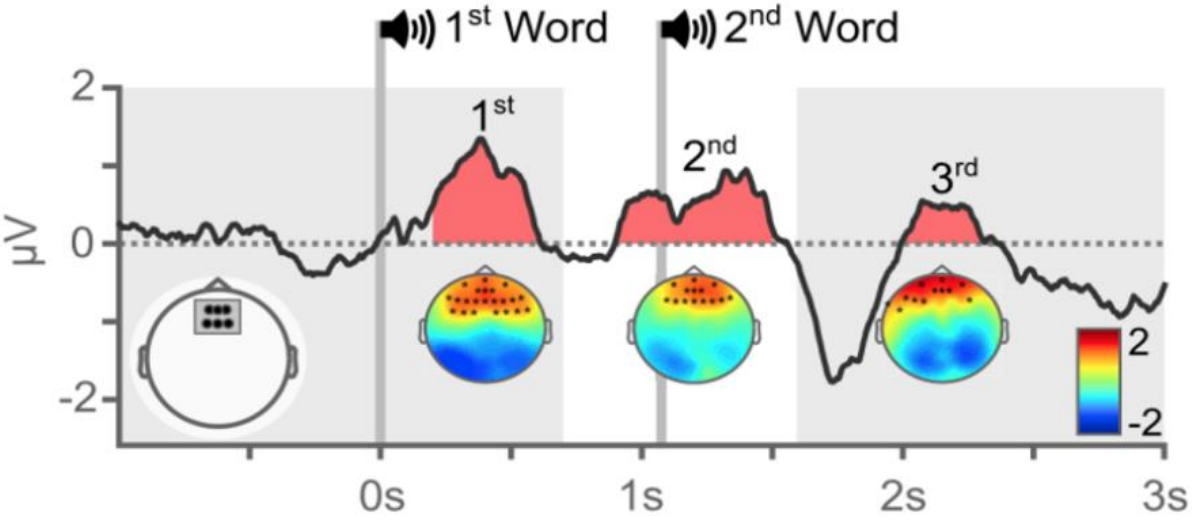


Figure 20 **Entrainment of slow waves following stimulus presentation in Züst and colleagues (2019).** Word pairs entrained slow waves inducing a first peak at 200–600 ms, a second peak at 900–1,500 ms, and a third peak at 2,000–2,300 ms (windows of interest are highlighted in red). Topographic maps indicate the electrodes that exhibited a significant peak (cluster-level Monte Carlo $p < 0.05$ for all three-time windows). From Züst et al., 2019

learning process. Later in the learning process, patterns of response differentiating correct and error trials are found after stimulus offset. **Such response might indicate the formation of a brain network that would resonate more strongly after the end of stimulus presentation during correct trials as compared to error trials and would reflect associative learning.**

The course of the learning process is here confounded with the night course. Thus, structural changes in sleep patterns, such as a higher propensity of SWA in early NREM sleep as compared to late NREM sleep periods, might confound our results (Nir et al., 2011). Contrary to this hypothesis, the activity evoked by our stimulation show that enhanced slow-wave activity is observed in late sleep. Moreover, the occurrence of K-complexes associated with the slow-wave rhythm during light NREM sleep are unchanged throughout the night (Nir et al., 2011). **This goes against the hypothesis that differences in the propensity for slow waves or K-complexes could explain the dynamics of neural responses**. Overall, the pattern of neural responses predicting memory performance supports the formation of associative memory during NREM sleep, in line with previous literature (Züst et al., 2019; Canales-Johnson et al., 2020).

3.4.4 Conclusion

Our results show that semantic associations can be formed during sleep and completes in many respects previous findings. It extends associative learning of linguistic stimuli to light NREM sleep and confirms the critical involvement of slow-wave activity in the learning process. It adds strong evidence that sleep learning is implicit. Yet, whether it is possible to form high-level semantic associations during REM sleep remains unresolved. The question whether sleep learning in this sleep state would lead to an explicit rather than implicit memory remains also to be tested.

4 STUDY 2 – SELECTIVE SUPPRESSION OF INFORMATIVE SPEECH DURING RAPID EYE MOVEMENTS

Hypothesis:

Informative stimuli are selectively processed during tonic REM sleep, but would be selectively gated during phasic REM sleep

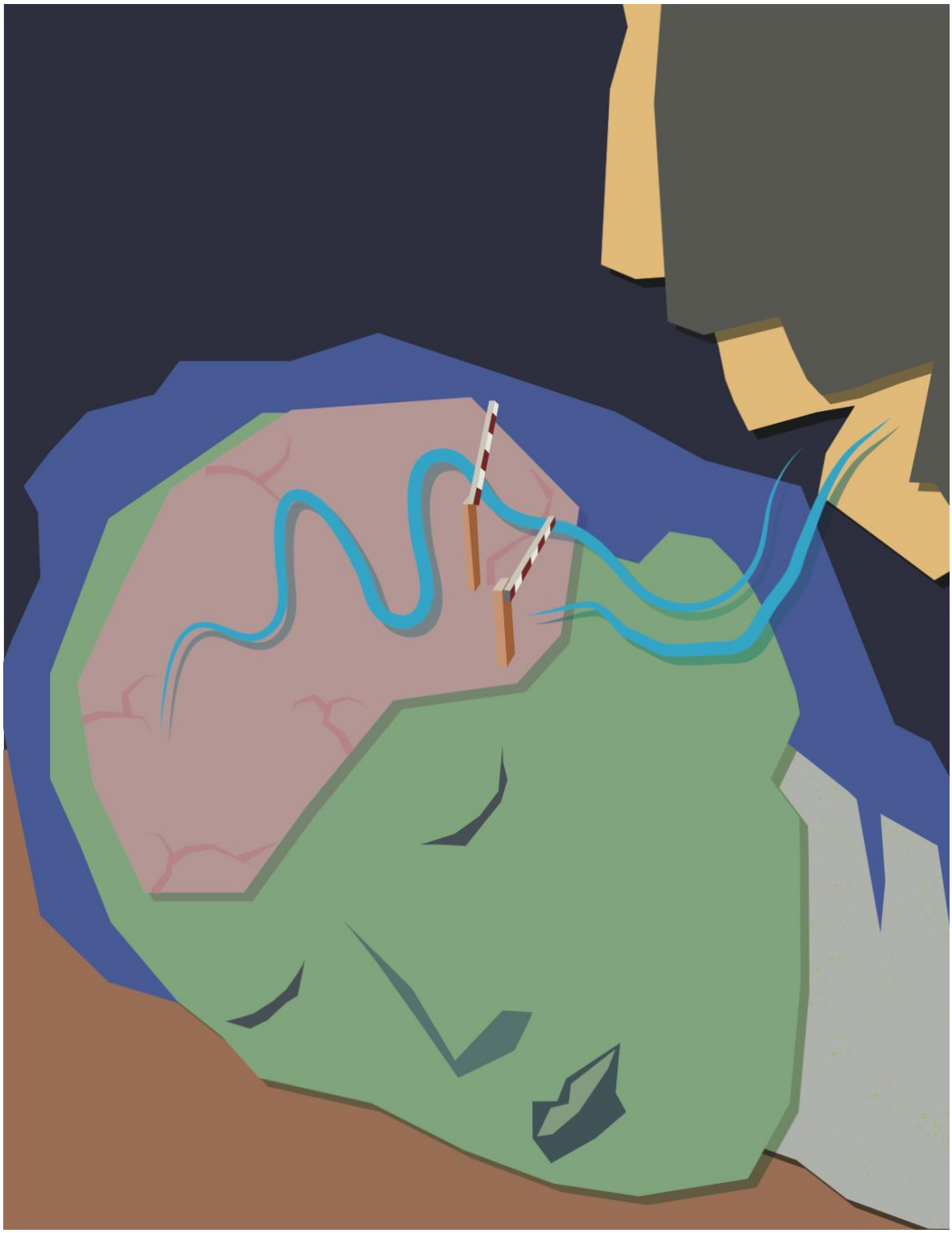
Related works:

Sleepers track informative speech in a multitalker environment

(3rd author, 2019, Nature Human Behavior)

Sleepers selectively suppress informative speech during rapid eye movements

(1st author, accepted, Current Biology)



Cover proposal to PNAS © Laure Koroma

4.1 Introduction

4.1.1 Sensory disconnection during REM sleep

Every night, we stop interacting with the outside world after falling asleep. This disconnection is typically reflected in dreams as we experience an alternative reality in which little, if any, external stimulation is incorporated (Dement & Wolpert, 1958; Berger, 1963; Rechtschaffen & Foulkes, 1965). Dreaming has been associated, but not exclusively, with rapid eye-movement (REM) sleep, a period when brain activity is the closest to wakefulness (Dement & Kleitman, 1957). **While the function of dreaming remains debated, decoupling from the external world may be crucial to avoid interference on dreaming activity** (Nir & Tononi, 2010).

However, a total disconnection from an ever-changing environment may prevent the sleeper from promptly responding to informative events (e.g., threat signals). **In fact, neural responses to external sounds in the auditory cortex are preserved during REM sleep** (Issa & Wang, 2011; Nir et al., 2015) Moreover, informative stimuli remain preferentially processed, as revealed by enhanced neural responses to one's own name compared to another name (Perrin et al., 1999; Blume et al., 2018; Figure 21). Other studies highlight the preservation of complex processing of the environment during REM sleep, such as the detection of expectation violations (Brualla et al., 1998; Bastuji et al., 2002; Strauss et al., 2015), semantic categorization (Andrillon et al., 2016), sensory conditioning (Arzi et al., 2014; Arzi et al., 2012) and perceptual learning (Andrillon et al., 2017). Yet, it remains unclear how much dreaming is associated with the gating of external stimuli.

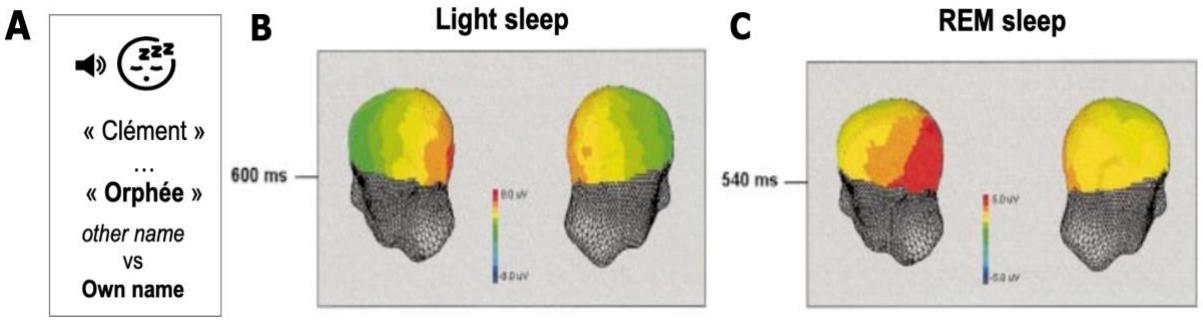


Figure 21 **Differential brain response to own one's name compared someone's else name.** (**A**) Schematic representation of the experimental paradigm.
(**B,C**) Brain response in light NREM sleep (B) and REM sleep (C) for the contrast own name vs. someone's else name. From Perrin et al., 1999

In particular, it remains unsettled how the brain dynamically balances between the need to focus on internal processes that occur during dream activity and the monitoring of informative stimuli. One way to resolve this issue is to consider the distinction between phasic REM (pREM) sleep which is characterized by the presence of eye movements (EMs) and tonic REM (tREM) sleep that is devoid of EMs. **Indeed, substantial literature investigating neural processes during eye movement indicates a link between EMs and dreaming activity** (see Hong and colleagues (2018) for a recent review) (Hong et al., 2018).

4.1.2 The balance of internal vs. external processing during REM sleep

Differences in auditory processing between pREM and tREM have been investigated. Arousal thresholds turn out to be lower during tREM sleep as compared to pREM sleep, revealing a stronger responsiveness to external stimuli in the absence of EMs (Ermis et al., 2010). Functional neuroimaging shows that the neural responsiveness to auditory stimuli in thalamo-cortical networks is abolished during EMs (Wehrle et al., 2007). Interestingly, auditory stimulation were conversely found to reduce the amount of EMs (Wehrle et al., 2007; Stuart & Conduit, 2009). This suggests that pREM and auditory processing might be mutually exclusive.

The competition between internal and external processing during pREM has found further support in neuroimaging studies. The activity in higher-order cortices associated with spontaneous cognition correlates negatively with the activity of sensory areas during REM sleep (Chow et al., 2013). **Additionally, a thalamo-cortical network is specifically active during pREM and was hypothesized to endorse the role of sleep protection by preventing sensory signals from interfering with internal activity** (Llinás & Paré, 1991; Wehrle et al., 2007)

How the presence of EMs affects the selective processing of auditory stimuli has been also studied. **Relying on an oddball paradigm, enhanced responses to deviant tones were found reduced in pREM compared to tREM** (Sallinen et al., 1996). Here, we adapted a cocktail-party paradigm during which auditory processing was continuously decoded from neural activity (Legendre et al., 2019, Appendix 5). We hypothesized that the presence of EMs would selectively prevent the processing of informative stimuli, whereas periods of REM sleep devoid of EMs would be associated with the monitoring of external signals. Using two speech streams in competition, we will be able to additionally test whether the presence of EMs gates sensory processing as a whole or selectively suppresses informative stimuli.

4.1.3 Continuous neural tracking of selective processing

In this paradigm, two speech streams are presented simultaneously. One stream, played in one ear, is meaningful (e.g., informative speech), while the other stream, played in the other ear, had normal syntactic and phonological properties but was meaningless (i.e., Jabberwocky speech as in Lewis Carroll's Jabberwocky poem). **We tracked speech processing by using a stimulus reconstruction approach, which allows for the continuous reconstruction of a sound's envelope based on its neural responses** (Mesgarani & Chang, 2012; O'Sullivan et al., 2015).

To ensure that this technique could adequately track attention orientation in our paradigm, we performed a control study at wakefulness (Legendre et al., 2019). We asked participants to focus either on informative speech or on Jabberwocky speech on a trial-by-trial basis. **We showed that attending either to the informative or Jabberwocky speech leads to higher reconstruction score for the attended stream and thus confirms that this technique allows to track attentional orientation** (Figure 22).

In an afternoon nap session, participants were instructed to focus only on the informative stream and then enter non-rapid eye movement (NREM) sleep. EEG markers reveal that informative speech is overall enhanced, but it is specifically suppressed during slow waves (Legendre et al., 2019). **Here, we used the same approach in morning naps to evaluate whether informative speech is preferentially processed during REM sleep, and selectively suppressed in presence of EMs.**

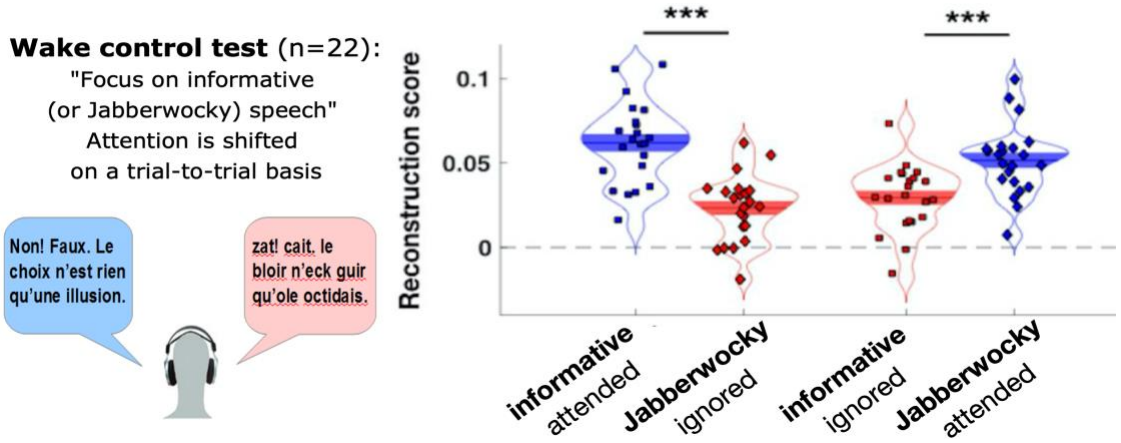


Figure 22 **Neural tracking of selective processing using the stimulus reconstruction technique.** Reconstruction scores were enhanced for attended stream regardless of story type. Dark mid-bars and surrounding shaded areas represent the mean ± the standard error of the mean of the distribution. Stars show the significance level of the signed rank test (***, $p<0.005$).

4.2 Methods

4.2.1 Material and procedure

Stimuli used for this study were identical to Legendre and colleagues (Legendre et al., 2019). Eighty meaningful (informative) and meaningless (Jabberwocky) stories which content words (e.g., nouns and verbs) were replaced by French pseudo words were matched in length, syntax, word frequency and phonemic properties. Stories were generated using a state-of-the-art Text-to-speech MATLAB software (Obin, 2011). Using the IRCAMTRAX module of Logic Pro software (Apple Inc.), the voice was manipulated to generate two copies of each story, one pronounced by a low-pitched voice and one by a high-pitched voice. Eighty pairs of informative and Jabberwocky were formed and matched in duration and intensity (73.57± 5.16 seconds, mean ± SD across stories, min: 54.04 seconds, max: 83.51 seconds).

42 French-native speakers (mean: 25.1 years old, min: 18, max: 31, 17 females) with self-declared normal hearing and no history of sleep disorders were recruited for this study. Easy sleepers (Epworth Sleepiness score, mean: 12.5, min: 10, max: 15) with normal or evening chronotypes (Morningness-eveningness score, mean: 42.1, min: 31, max: 54) were selected through online questionnaires. **To increase sleepiness and ensure high REM sleep pressure during the experiment, participants were required to sleep about 30% less during the night preceding the experiment (verified with actimetry) and to arrive at 7.30 a.m. at the sleep laboratory**. They were also deprived from stimulants (e.g., caffeine) the day of the experiment.

During the entire experiment, participants laid down in a dark, isolated room equipped with 64-channel EEG gel-nets (EGI system, Electrical Geodesic Inc.) and chin-EMG (Figure 23). Stimuli were delivered to participants using non-electrical earplugs (RLINK Ear Tone 3A, 10 Ohms, Interacoustic Inc.) and played using an Echo Fire 12 Soundcard (Echo Digital Audio Corp., Santa Barbara, CA, USA). **The volume of stimulation was set around 50 dB and adapted to participant's preferences, as in previous studies** (Andrillon et al., 2017; Strauss et al., 2015). The side of the stimulation (left or right ear) and the pitch of the voice (low and high pitch) of the informative speech was randomized trial-by-trial and counterbalanced for each pair across participants. Details of the experimental procedure is presented in Figure 23.

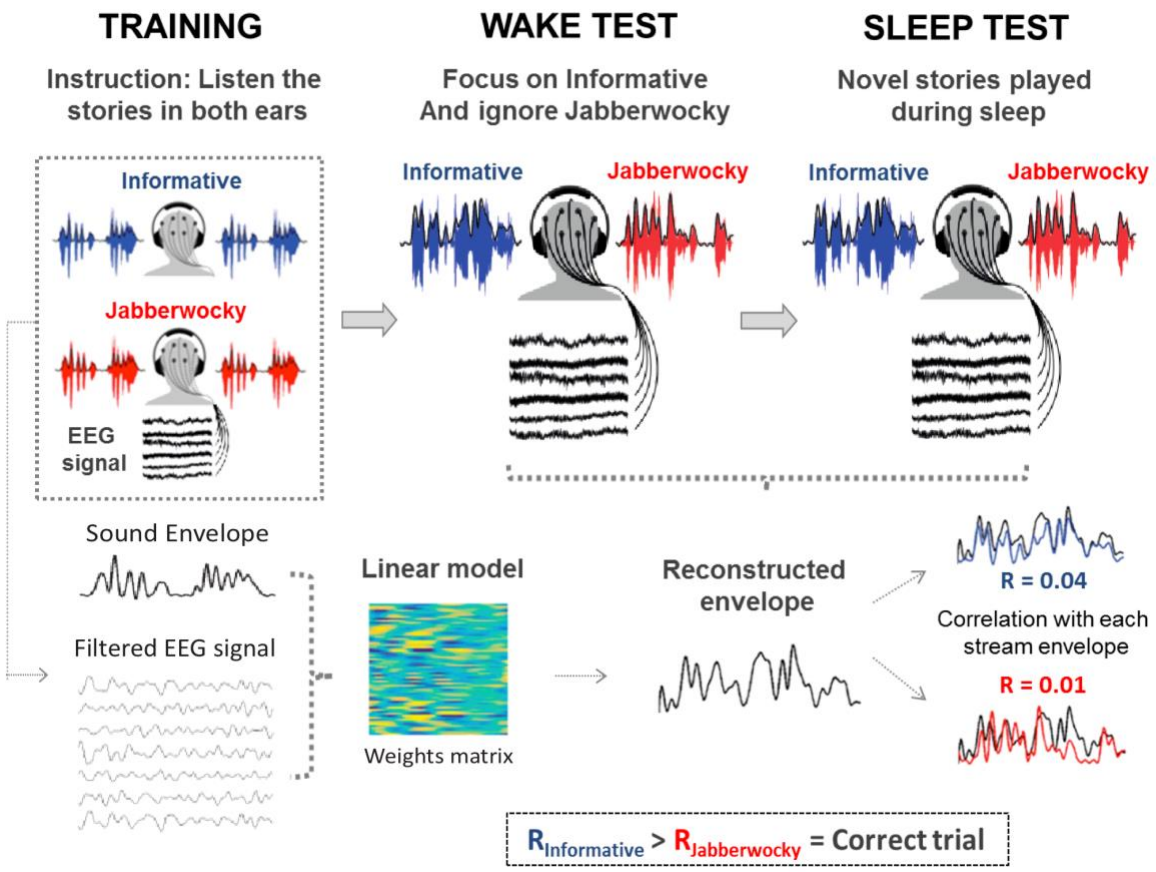


Figure 23 **Morning nap cocktail-party paradigm.** First, participants listened to 12 stories in both ears, 6 informative stories followed by 6 Jabberwocky stories ('Training phase'). Then, participants were instructed to focus on the informative story that was played in one ear while ignoring the Jabberwocky story that was played in the other ear ('Test phase'). After 8 trials during which participants had to perform the task in wakefulness ('Wake Test phase'), participants were allowed to fall asleep while the trials from the wake test phase were continuously played ('Sleep Test phase': ~90 minutes). Novel informative (blue) and Jabberwocky (red) stories were played whenever participants were visually scored as being asleep by two trained scorers (MK and CL). To track speech processing using cerebral activity, training trials were used to map the EEG response to variations of the sound envelope. The obtained linear model was then used to reconstruct a sound envelope from the filtered EEG recorded during wakefulness and sleep test trials. A correlation score was computed by comparing the predicted sound envelope with the envelope of each auditory stream. The trials with a higher reconstruction score for the informative speech compared to the Jabberwocky speech were scored as correct and the percentage of correct trials per condition defined the decoding performance. During the Training phase, trials were self-paced while during the Test phase, trials were separated with jitters of 4 to 6s (random uniform distribution).

4.2.2 Preprocessing

EEG signals were amplified (NetAmp 300), referenced online to Cz and sampled at 500 Hz. EOG and chin EMG were also recorded. EEG recordings and audio stimuli were synchronized using a third audio channel through which a tone was played at the onset and end of each trial and recorded by the amplifier (NetAmp 300). EEG and EOG signals were re-referenced to mastoids and bandpass filtered between 0.1 and 30 Hz (two-pass Butterworth filter, 5th order). **EMG signal were derived locally and bandpass filtered between 80 and 160 Hz (two-pass Butterworth filter, 5th order).**

Vigilance states were scored offline on 20s-long windows by trained scorers (MK and CL) and confirmed by an expert scorer (DL) following established guidelines (Iber, 2007) (Figure 24 for two example of sleep hypnograms). The size of the window was chosen based on previous experiments (Andrillon et al., 2016, 2017). For the sleeping Test phase, only novel trials containing novel stimuli (i.e., not played during wakefulness) were kept for analysis. Trials that contained a mixture of vigilance states were excluded from analysis. **Participants with less than 4 trials within REM sleep were discarded from further analyses, resulting in conserving 18 out of 42 participants** (number of trials in REM sleep, mean=10.8±1.5; Table 9)

Eye movements (EMs) were visually identified by trained scorers (MK and CL) blind to experimental conditions. EOG were re-referenced to the contralateral mastoid signals were bandpass filtered between 0.5 and 2 Hz (two-pass Butterworth filter, 5th order). Co-ocurrent deviations in left and right EOG were visually detected and the onset of the first deviation was marked as EM onset. **EMs were further visually classified into two categories: "isolated" when EMs were followed by no more than one EM and "burst" when EMs were followed or preceded by at least two other EMs.** We further distinguished burst onset, defined as the absence of bursts in the 12 preceding seconds, and the burst offsets, defined as the absence of burst in the 12 successive seconds. Finally, we redefined our 20s-scoring windows as phasic REM sleep (pREM) if they contained burst EMs, and tonic REM sleep (tREM) otherwise. In agreement with the literature, we obtained ~20% of pREM sleep (Spreng et al., 1968; Arnulf, 2011). Participants with more than 4 scoring windows of one type were conserved for analysis (n=18 for tonic REM, 24±2.4 windows, n=8 for phasic REM, 18±5.1 windows). Finally, brain signals corresponding to EM artifacts during REM sleep were identified using Independent Component

Analysis (ICA) using EEGLAB (Delorme & Makeig, 2004). Visually-selected components were removed from the EEG signal for trials during REM sleep.

Table 9 **Sleep statistics during the morning nap**. Sleep efficiency was calculated as the percentage of time spent in NREM1, NREM2, NREM3 or REM sleep during the sleep phase. The number of awakenings refers to the number of transitions from consolidated sleep (NREM2, NREM3 or REM sleep) to wakefulness. The number of state transitions was computed as the number of changes in the scoring of vigilance states. The sleep onset latency was defined as the first apparition of stage NREM2 since the beginning of the sleep phase. The percentage of tonic REM sleep was computed as the number of scoring windows of 20s classified as tonic REM sleep, i.e., devoid of burst eye movements, divided by the total number of scoring windows scored as REM sleep. Eye-movement density corresponds to the number of eye movements detected per minute spent in REM sleep.

	Total sleep time (min)	**Sleep efficiency (% of the session spent asleep)**	**Sleep onset latency (min)**	**Duration of REM sleep (min)**	**Percentage of tonic REM (%)**	**Eye-movement density (.min^{-1} in REM sleep)**
Mean±SEM	91.5±4.4	70±1.8	24.8±2.3	18.4±1.8	79.9±5.3	6.0±1.2

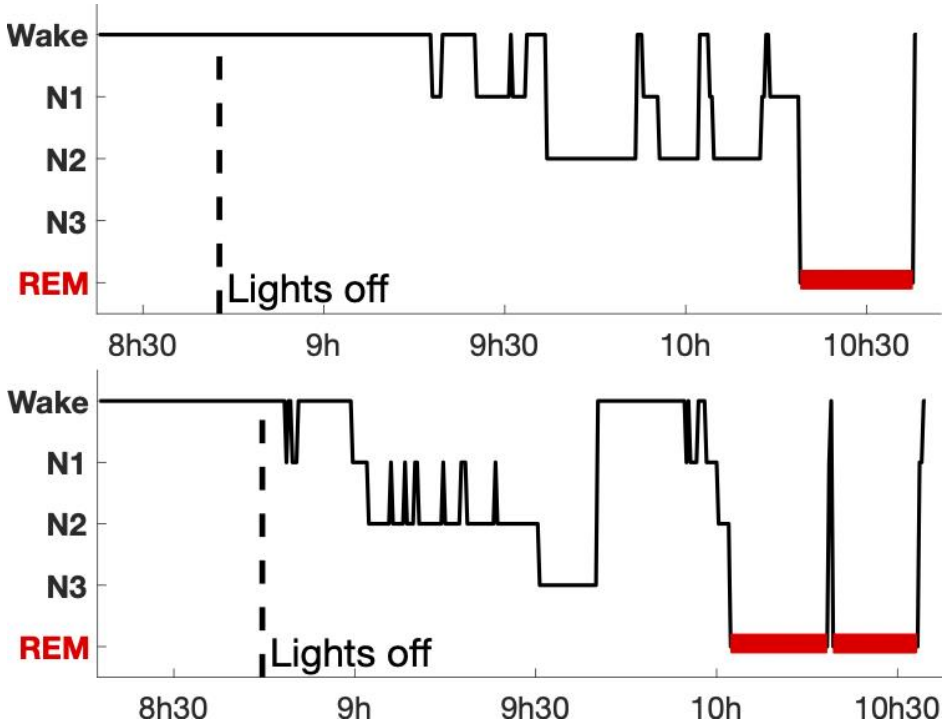


Figure 24 **Morning nap hypnograms from two participants.** The experiment was stopped after *circa* 90 minutes of sleep (i.e., roughly one sleep cycle) upon awakening or entering a light sleep.

4.2.3 Stimulus reconstruction

The Training phase consists in building an optimal linear model of how the brain response (here the EEG envelope of the 64 channels) reacts to variations in the auditory stimulation (here the auditory envelope). This model was trained on trials of the Training phase (6 informative stories then 6 Jabberwocky stories played in both ears). Because the brain processes auditory signals with different time delays (referred to as time-lags), we first identified the range of time-lags during which auditory signals are processed. To do so, we used detrended EEG signal to avoid any filtering artifacts. Using trials from the Training phase, we reconstructed the auditory input at individual time-lags using a leave-one-out procedure (i.e., training the model on 11 trials and testing on the remaining trial, successively for every trial of the Training phase of each participant). **The reconstruction score for each trial and each time-lag was defined as the Pearson's correlation between the envelope reconstructed from the EEG signal and the envelope of the acoustic input**. The reconstruction scores were averaged within participants for each time-lag and compared to 0. The cluster of time-lags with reconstruction scores significantly above 0 ranged from -190 ms to 840 ms and was selected for subsequent analyses (Figure 25A).

Then, the EEG signal was re-referenced to the average of all sensors and high-pass filtered at 0.5 Hz and low-pass filtered at 8 Hz (two pass Butterworth filter, 5th order) using the fieldtrip toolbox (Oostenveld et al., 2011). The sound envelope of each auditory stream of the corresponding trial was extracted with the Hilbert transform and was filtered below 8 Hz (two pass Butterworth filter, 5th order). Both EEG and auditory signals were then down sampled at 100 Hz. We first verified that our model was not biased towards any stimulus category. To do so, the stimulus reconstruction was performed on Training trials using the aforementioned leave-one-out procedure and using time lags defined previously (190ms to 840ms). **Reconstruction scores revealed no difference between informative and Jabberwocky speech** (informative vs. Jabberwocky, non-significant, Bayes Factor: 3.80; Figure 25B). Then, we performed the stimulus reconstruction on Test trials. The reconstructed envelope was compared to the envelope of each auditory stream using Pearson's correlation. For each trial, this resulted in a reconstruction score for each type of speech: $r_{informative}$ and $r_{Jabberwocky}$. Attention was defined as correct, i.e., being oriented towards the informative speech, if $r_{informative}$ was higher than $r_{Jabberwocky}$ (i.e., the reconstructed envelope was closer to the envelope of the informative speech). The percentage of trials with a higher reconstruction score for the informative speech as compared to the Jabberwocky speech refers to the decoding performance (%).

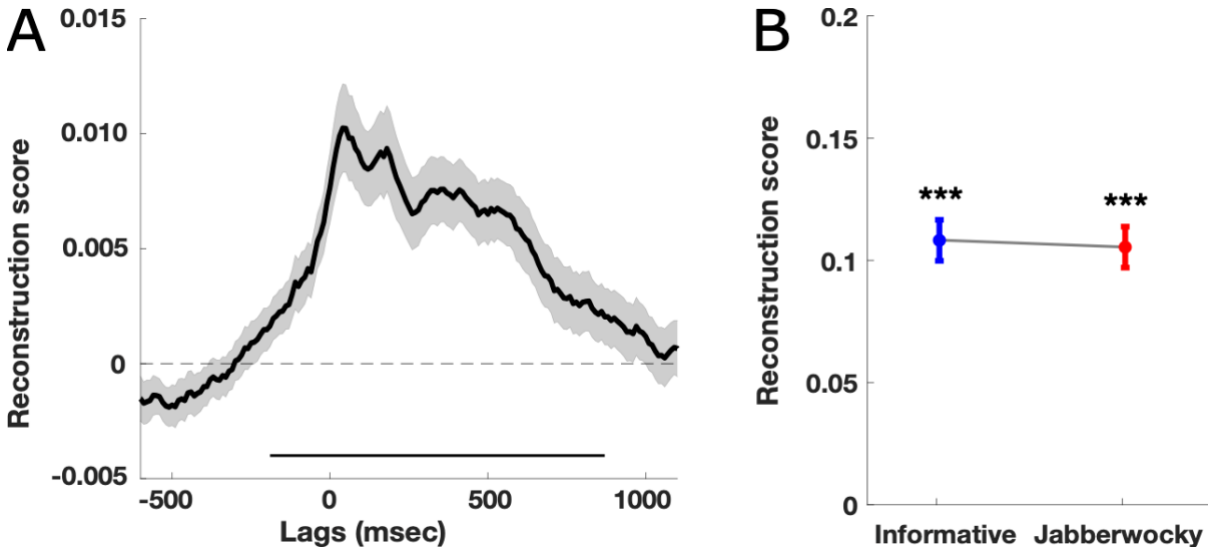


Figure 25 **Construction of an unbiased model for stimulus reconstruction**

(A) A reconstruction model was trained and tested for each individual lag on trials from the Training phase. EEG data were first detrended to avoid any resulting filtering artefacts. 11 out of 12 trials from the Training phase were selected to train the reconstruction model that was tested on the remaining trial following a leave-one-out procedure. Results for each lag were averaged across participants (N=18). Mean and standard error to the mean (SEM) are represented respectively with a solid line and shaded area. Horizontal bar denotes the significant cluster of lags for which reconstruction scores differ from 0. A significant cluster ([-190, 870] ms) was identified, defining the time-lags used for subsequent analyses. (**B**) Reconstruction scores obtained separately for informative and Jabberwocky speech tested on Training trials using a leave-one-out procedure. Mean and SEM across participants are represented as respectively filled circles and solid vertical lines. Models were significantly different from 0 (***, P<0.001) for both types of speech but were not different from one another (P>0.05).

Reconstruction scores were also computed on scoring windows of 20 seconds to compare tREM and pREM sleep. It was computed on the first half (0-30s) or second (30s-60s) half of trials to investigate within-trial dynamics. **Additionally, time-course of speech processing was studied by computing reconstruction scores using sliding windows**. Their duration was 10s with 500ms steps to investigate intra-trial dynamics. It was 4s with 100ms steps to study sensory processing around EMs (onset at t=0s; windows computed from -10s to +10s). Time-courses of reconstruction scores were averaged across participants with at least 4 detected micro-events per condition (n = 14 for all and isolated EMs, 7 for the onset and offset of bursts). Time-courses were smoothed for visualization purposes only using a 500-ms-wide Gaussian kernel, but statistical tests were performed on the reconstruction scores before smoothing.

Pearson's R was used as a parametric measure of the correlation between the reconstructed envelope and the auditory stimuli, resulting in a reconstruction score for each stream (Legendre et al., 2019). Reconstruction scores between speech streams and across sleep stages, as well as decoding performance across sleep stages, were compared using non-parametric paired statistics (Wilcoxon signed rank test). Bonferroni correction for multiple comparisons was applied for post-hoc tests. Effect sizes calculated following the formula: $r = Z/\sqrt{n}$, where z is the z-stats of the Wilcoxon signed rank test and n the number of data-points. **In case of non-significant results, Bayesian statistics were computed using the bayesFactor toolbox in Matlab** (Krekelberg, 2019). A Bayes Factor above 3 typically provides supportive evidence for the null hypothesis. Linear mixed-effect models were performed using Matlab fitlme function to evaluate the interactions between experimental conditions on reconstruction scores and decoding performances. This technique allows comparisons between unbalanced datasets among conditions and across participants with heterogeneous sleep patterns. All dependent variables were defined as categorical values. When comparing time series of reconstruction scores, we relied on non-parametric cluster permutation statistics to control for multiple comparisons. Clusters were defined as consecutive time-points for which parametric t-tests reached a specific threshold (α=0.05). For each cluster, the sum of t-values was compared to the maximum cluster statistics obtained after random permutation of the conditions considered (n = 1000 permutations). We computed a Monte-Carlo P-value (referred to as $P_{cluster}$). For each significant cluster, the average Cohen's d (mean over standard deviation) was calculated for each participant and was reported as the effect-size.

4.3 Results

4.3.1 Maintenance of selective processing during REM sleep

We first found that both informative speech and Jabberwocky speech could be reconstructed across wakefulness, light NREM sleep and REM sleep, revealing preserved auditory encoding across vigilance states (Figure 26A, $p<0.05$ for all conditions corrected for multiple comparisons). We thus replicated with this independent dataset our previous results that informative speech was preferentially reconstructed over Jabberwocky during wakefulness and light NREM sleep (informative vs. Jabberwocky for wake: $r=0.85$, $P<0.001$ and light NREM sleep: $z=0.51$, $P<0.05$; Figure 26A). **We additionally show that these results extend to REM sleep** (informative vs. Jabberwocky: $r=0.65$, $P<0.01$; Figure 26A). This result was confirmed when performing stimulus reconstruction on individual time-lags. Clusters of time lags for which informative speech is preferentially processed were found in all vigilance states (Figure 26B-D).

Then, we computed a decoding score corresponding to the proportion of trials with a higher reconstruction score for informative speech as compared to Jabberwocky speech. **We found that decoding performance was significantly above the chance level of 50% for both wakefulness and REM sleep** (wake: $z=0.82$, $P<0.001$; and REM: $z=0.61$, $P<0.01$; Figure 26E). Yet, decoding performance was lower in REM sleep than during wakefulness, suggesting the existence of a gating mechanism during REM sleep (wake vs. REM sleep: $r=0.68$, $P<0.001$; Figure 26E).

To investigate whether this difference resulted from the disruption of auditory encoding for all streams or more specifically for informative speech, we compared reconstruction scores for informative and Jabberwocky speech separately. We first found that informative speech and Jabberwocky speech are differently affected across wakefulness and REM sleep ($t(677.35)=-4.41$, $P<0.001$ for the interaction informative vs Jabberwocky x wake vs REM sleep). **Post-hoc analyses revealed that the reconstruction of informative speech was selectively modulated by the transition to REM sleep** (wake vs REM sleep: $r=0.68$, $P<0.01$; Figure 26F), while Jabberwocky speech remained unaffected (wake vs REM sleep, non-significant, Bayes Factor: 3.64; Figure 26F). Thus, decreased decoding performance during REM sleep appears to be linked to a selective reduction in the processing of informative speech, rather than a general decline in the encoding of auditory signals.

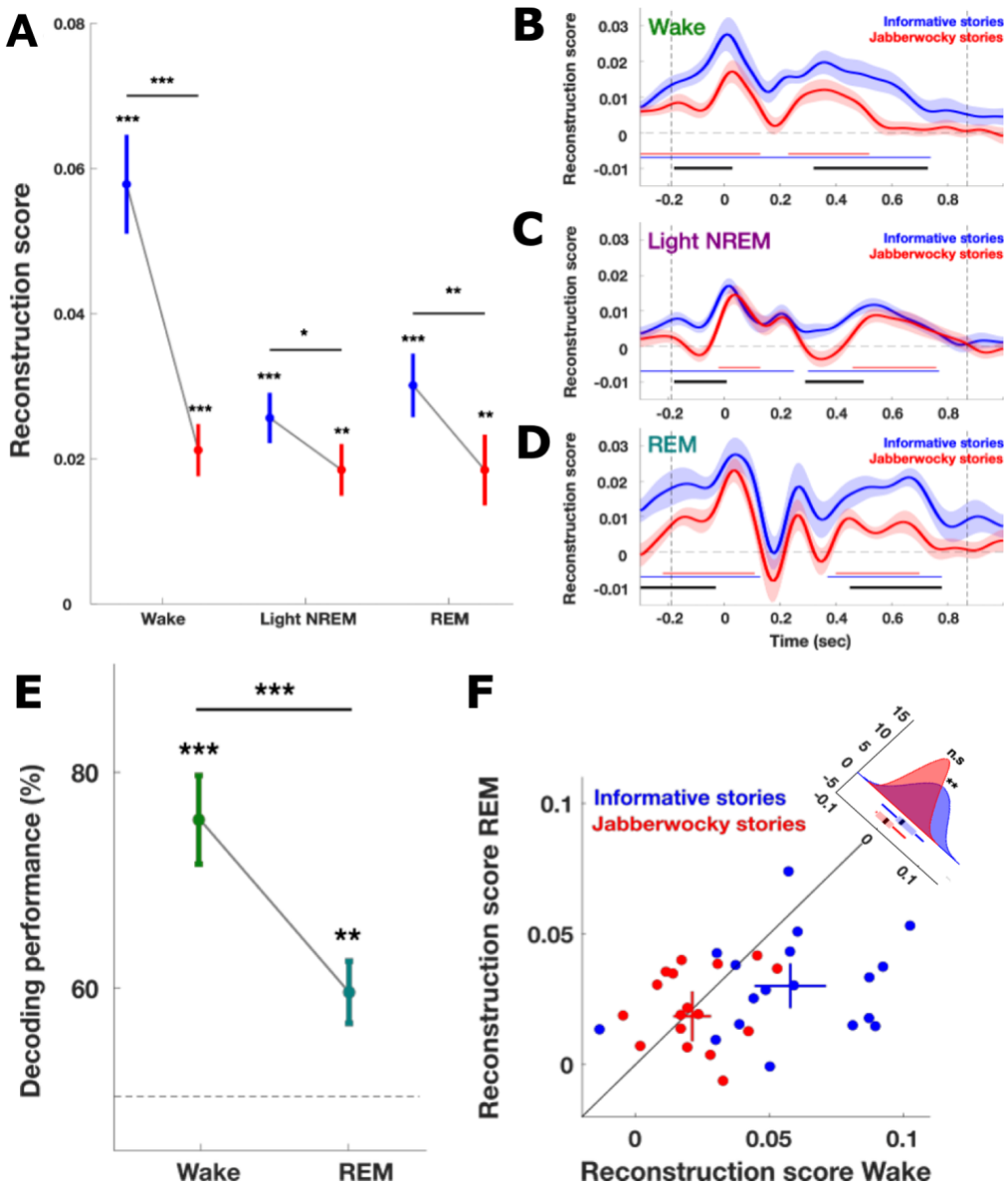


Figure 26 **Preserved selective processing of informative speech across vigilance states.** (**A**) Processing of informative (blue) and Jabberwocky (red) speech across vigilance states. (**B-D**) Contribution of individual time lags to the processing of the informative and the Jabberwocky speech across wakefulness (**B**), light NREM sleep (**C**) and REM sleep (**D**). (**E**) Decoding performance during wakefulness and REM sleep.

(**F**) Individual reconstruction scores for each story type across vigilance states (N=18). Across all figures, mean and standard error to the mean across participants (N=18) are represented and stars show significance levels against 0 or across conditions (***: P<0.001, **: P<0.01, *: P<0.05). For (B-D), bars denote significant clusters (see Methods) for which reconstruction scores of informative (blue) and Jabberwocky (red) speech differ from 0, as well as informative from Jabberwocky speech (black). In (F), under the distribution curves, solid black lines represent the mean, shaded areas mark the first and third quartiles, and solid lines represent the whiskers.

4.3.2 Selective suppression of informative speech in presence of eye movements

We then tested whether rapid eye movements (EMs), a marker of oneiric activity which occurs during REM sleep, are associated with the selective gating of informative speech. We removed EMs related activity from EEG using ICA to avoid muscular contamination of speech reconstruction (see *Methods*). **Our analyses revealed an inverse correlation between the number of EMs per trial and the reconstruction of informative speech** ($P<0.001$; Figure 27A). **Crucially, this was not the case for Jabberwocky speech** ($P>0.05$; Figure 27B). This suggests that EMs do not affect the processing of Jabberwocky speech and additionally reinforces that EMs related artifacts may not impact the quality of stimulus reconstruction. It also suggests that the presence of eye movements selectively modulates the processing of informative signals.

We then inspected more systematically the distinction between tonic (tREM) and phasic (pREM) REM sleep. Congruent with the results above, we found that the selective processing of informative speech is distinct during pREM and tREM sleep ($t(1198)=-2.07$, $P<0.05$ for the interaction tonic vs. phasic REM x informative vs. Jabberwocky speech; Figure 27C). **Post-hoc analyses revealed that the selective amplification of informative speech was present during tREM sleep** (informative vs. Jabberwocky: $r=0.55$, $P<0.05$), **but absent during pREM sleep** (not-significant, Bayes Factor: 5.36). These analyses confirm that periods of sustained eye movement activity prevent the preferential processing of informative speech. To confirm this interpretation, we investigated the temporal relationship between the occurrence of EMs and the selective gating of informative speech by performing a time-resolved analysis of reconstruction scores around EMs. Within a 10s window around the onset of EMs, we found that informative speech was amplified before EMs ([-7.8, -2.8]s, $d=0.63$, $P_{cluster}<0.05$), but this effect disappeared during and after EMs (Figure 27D). Contrastingly, no such modulation could be evidenced for Jabberwocky speech. As EMs can occur in bursts, the reconstruction around a given EM may be impacted by the presence of surrounding EMs. To test for this potential contamination, we investigated the time-course of reconstruction score at the beginning and end of burst EMs. Our analysis revealed that the amplification of informative speech was present before the beginning of bursts and then disappeared at their onsets ([-4.6, -0.2]s, $d=1.48$, $P<0.001$; Figure 27F). Conversely, we observed that the amplification of informative speech was regained only after burst offsets ([5.0, 7.5]s, $d=0.98$, $P<0.05$; Figure 27G). We then refined our analysis by inspecting isolated EMs (i.e., with no more than one additional EM nearby). We compared reconstruction scores obtained at the onset of isolated EMs with that computed on the entire REM sleep period.

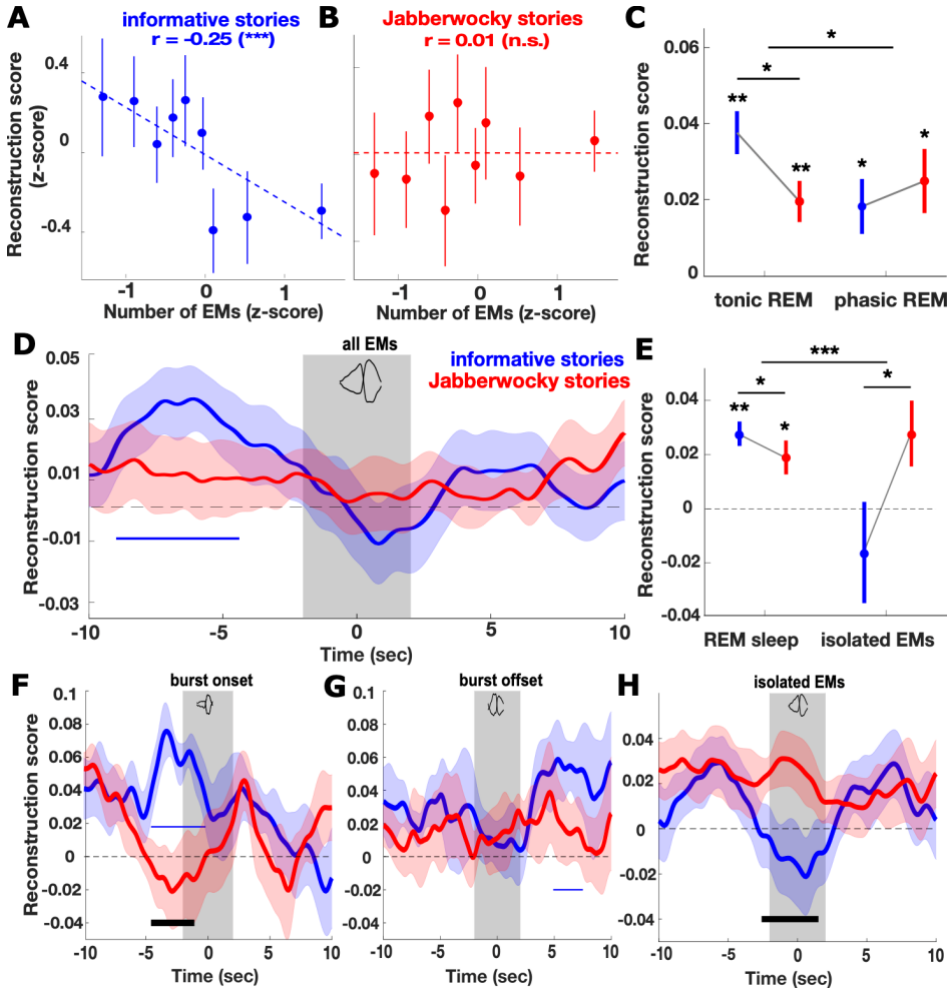


Figure 27 **Selective suppression of informative speech during eye movements**

(**A-B**) Correlation between the amount of eye movements (EMs) per trial and the reconstruction scores for the informative (A) but not for the Jabberwocky (B) speech. Values were z-scored for each participant (N=18) and binned for visual purposes (n=10 bins on the sorted number of EMs). Dotted lines are the linear regression between variables (n.s., not-significant; ***: P<0.001)

(**C**) Reconstruction scores in tREM (N =18) and pREM (N = 8).

(**D**) Time-course of reconstruction score around the onset of all EMs (t=0s) (N=14).

(**E**) Reconstruction scores at the onset of isolated EMs or on the entire REM sleep (N=14)

(**F,G,H**) Time-course of reconstruction score around the onset of bursts of EMs (N=7; E), the offset of burst of EMs (N=7; F) and at the onset of isolated EMs (N=14; G). For bar plots, mean and SEM are represented respectively as filled circles and solid vertical lines for informative (blue) and Jabberwocky (red) speech. Stars show significant difference against 0 and for interactions across story types and vigilance states (***: P<0.001, **: P<0.01, *: P<0.05). For time-courses, mean and SEM are represented respectively with solid lines and shaded areas. Horizontal bars denote significant clusters which differ from 0 for informative (blue) speech, and informative from Jabberwocky speech (black) (P<0.05 corrected for multiple comparisons).

We confirmed that the presence of isolated EMs was indeed modulating the selective processing of informative speech ($t(1180)=-3.52$, $P<0.001$ for the interaction informative vs. Jabberwocky x isolated EM vs. REM sleep; Figure 27E). **Post-hoc analyses revealed that informative speech was overall selectively amplified during REM sleep but selectively suppressed at the onset of isolated EMs** (informative vs. Jabberwocky in REM sleep: $z=0.50$, $P<0.05$; and during isolated EMs : $z=-0.84$, $P<0.05$; informative vs. 0 during REM sleep: $z=3.17$, $p<0.01$; Jabberwocky vs. 0 during REM sleep: $z=2.54$, $P<0.05$; Figure 27E). We then confirmed that such selective suppression of the informative stream was restricted to the period surrounding the onset of isolated EMs ([-2.6, 1.5]s, $d=-0.73$, $P_{cluster}<0.05$; Figure 27H). We also checked eye-movement artifacts removal was not responsible for our effects and obtained similar results with and without the ICA procedure (Koroma et al., 2020, Supplementary information Figure S3).

4.3.3 Delayed selective processing during REM sleep

We further investigated whether selective processing is sustained within a trial across vigilance states. Selective processing was sustained over the whole trial period during wakefulness ([17, 55]s, $d=0.59$, $P<0.001$; Figure 28A). **During REM sleep, we found that selective processing was yet restricted to the second half of trials** ([31.5, 42]s, $d=0.33$, $P<0.05$; Figure 28C). Light NREM sleep revealed only a trend for a decline of selective processing across time (Figure 28B). To better assess the dynamics of selective processing, we further separated the trials in the first and second half of trials (from 0 to 30s and from 30s to 60s of each trial).

We first found that dynamics of selective processing differed between light NREM and REM sleep ($t(136)=-3.75$, $p<0.001$, for the interaction informative vs Jabberwocky x light NREM sleep vs REM sleep x first vs second half; Figure 28D). We replicated previous findings that selective amplification of informative speech was restricted to the first half of trials during light NREM sleep ($t(68)=-2.01$, $p<0.05$, for the interaction informative vs Jabberwocky x first vs second half; informative vs Jabberwocky in the first half: $r=0.53$, $P<0.05$; Figure 28D) (Legendre et al., 2019). During REM sleep, the selective amplification of informative speech was restricted to the second half of trials ($t(68)= -3.55$, $p<0.001$, for the interaction informative vs Jabberwocky x first vs second half; informative vs Jabberwocky in the first half: $r=0.64$, $P<0.05$; Figure 28D). This was confirmed when investigating decoding performance computed on half of trials ($t(102)= 2.83$, $p<0.01$, for the interaction light NREM vs REM sleep x first vs second half; informative vs Jabberwocky in the second half of REM sleep: $r=0.54$, $P<0.05$; Figure 28E).

We then inspected whether this pattern was sensitive to the distinction between tREM and pREM. To do so, we further classified 20s-windows depending on whether they belonged to the first half or the second half of trials. We found that speech was encoded across all conditions ($p<0.05$, corrected for multiple comparisons; Figure 28F). **No interaction was found but post-hoc tests revealed a reversal of selective processing between the first and second half of stimulation in pREM** ($t(28)=-2.60$, $p<0.05$, for the interaction informative vs Jabberwocky x first vs second half; Figure 28F). No difference in the number of EMs between the first and second half of trials could explain this result (not-significant, Bayes Factor: 2.95; Figure 28G).

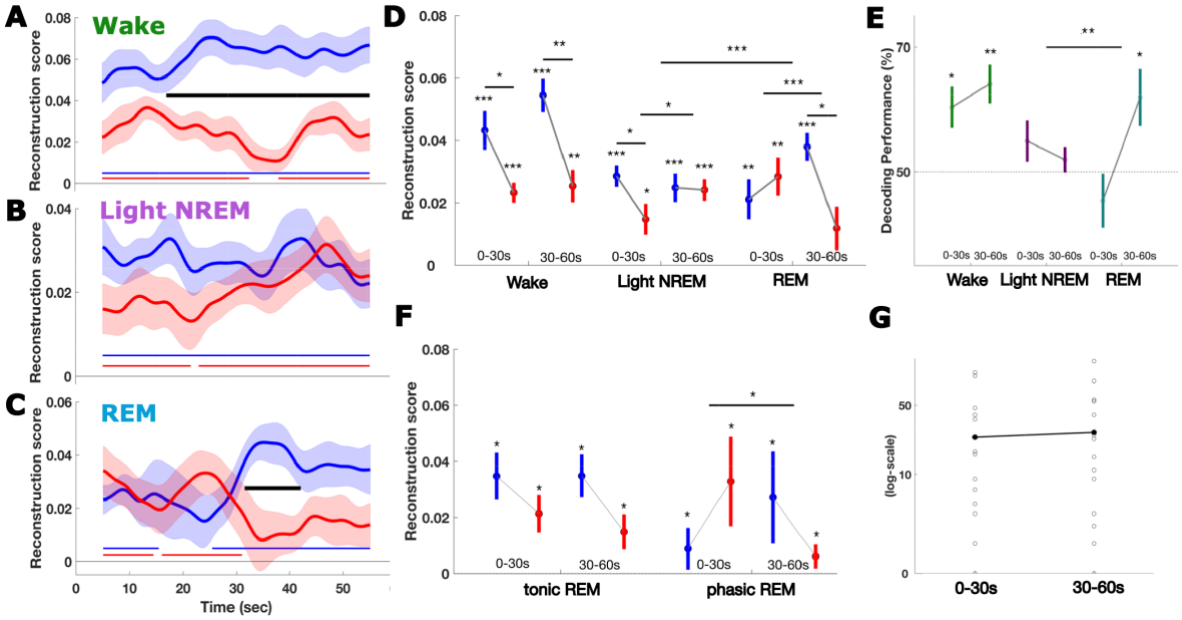


Figure 28 Intra-trial dynamics of selective processing across vigilance states.

(**A-C**) Time-course of reconstruction during wakefulness (A), light NREM (B) and REM sleep (C)

(**D**) Reconstruction in the first and second half of trials across vigilance states

(**E**) Decoding of selective processing in the first and second half of trials across vigilance states

(**F**) Reconstruction in the first and second half of trials across substages of REM sleep

(**G**) Repartition of eye movements in the first and second half of trials during REM sleep

For time-courses, mean and SEM are represented respectively with solid lines and shaded areas for informative (blue) and Jabberwocky (red) speech. Horizontal bars denote significant clusters for which reconstruction scores for informative (blue) speech and Jabberwocky (blue) speech differ from 0, and informative from Jabberwocky speech (black) ($P<0.05$ corrected for multiple comparisons). For bar plots, mean and SEM are represented respectively as filled circles and solid vertical lines. Stars show significant differences against 0 and for interactions across story types and vigilance states (***: $P<0.001$, **: $P<0.01$, *: $P<0.05$).

4.4 Discussion

4.4.1 Mechanism of the gating of external information during REM sleep

While the mechanisms underlying sensory disconnection have been relatively well studied during NREM sleep, such investigations have been so far limited for REM sleep (Nir & Tononi, 2010). It was hypothesized that thalamocortical oscillations gate the access of sensory inputs to cortical activity during deep NREM sleep, called the thalamic gating hypothesis (McCormick & Bal, 1994; Figure 29A). **In this study, we show evidence that sensory inputs remain encoded in cortical activity, suggesting that sensory inputs are not blocked at a thalamic level in REM sleep**.

Such a gating mechanism was later postulated to operate at a cortical rather than thalamic level and prevented the transmission of sensory information from primary sensory areas to higher-order associative regions (Nir & Tononi, 2010; Figure 29B). **The selective processing of speech streams differing in their semantic content suggests that associative regions are also involved in the selection of stimuli during REM sleep, ruling out this hypothesis**.

Attention was also suggested to be impaired during REM sleep, as in other altered states of consciousness such as hypnosis (Nir & Tononi, 2010). Yet, we found here that the selective processing of informative speech was maintained during REM sleep, even if reduced as compared to wakefulness. **Presenting competing auditory streams allowed us to show that informative stimuli can be flexibly enhanced or suppressed depending on the presence of EMs**. Since EMs are closely associated with internal activity such as PGO waves and oneiric activity, we propose the hypothesis that our results support the "informational gating" hypothesis, i.e., the competition for attentional resources by internal processing at the expense of external stimulus processing during REM sleep (Nir & Tononi, 2010; Andrillon et al., 2016; Figure 29C).

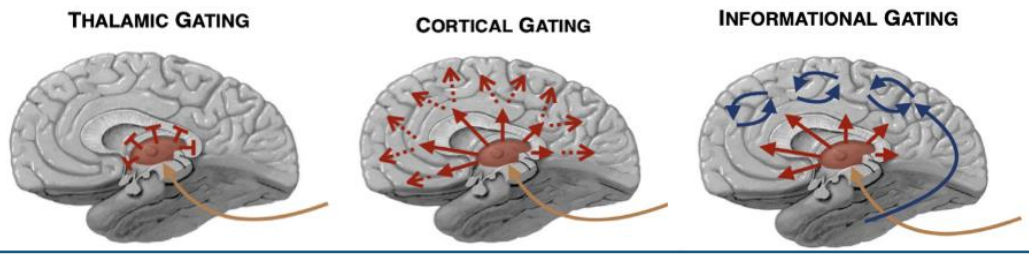


Figure 29 **Three mechanistic explanations of sensory gating during sleep**. Thalamic gating supposes a blockade of sensory processing at the thalamic level, cortical gating at a cortical level, while informational gating suppose that the blockade of external information depends on the uptake of attentional resources by internal processes. From Andrillon & Kouider, 2020

4.4.2 Selective suppression of informative speech during EMs

Indeed, the "informational gating" hypothesis suggests a pivotal role for selective processing in the balance between internal vs. external processing depending on stimulus properties (e.g., informative stimuli) and spontaneous activity (e.g., dreaming activity). Representations of competing speeches are encoded separately in the auditory cortex (Ding & Simon, 2012). This allows in our study for the selective processing of informative speech while leaving the Jabberwocky speech unaffected. Selective suppression during EMs may result from ongoing internal activity, such as dreaming or memory consolidation. **Dreaming has been associated with EMs, yet it has also been reported without EMs, during both REM and NREM sleep** (Stickgold et al., 2001; Siclari et al., 2013). Assessing the impact of other markers of dreaming activity (e.g., EEG spectral changes (Siclari et al., 2017)) on sensory processing should allow to investigate whether our results generalize to other correlates of dreaming.

Our study provides also further evidence for a close link between perceptual processing and sleep depth as demonstrated by arousal thresholds (Ermis et al., 2010; Figure 30A). Using the same paradigm, we previously found that the selective amplification of informative speech occurs during light NREM sleep but disappears in deep NREM sleep, with a selective suppression of informative speech during slow waves (Legendre et al., 2019; Figure 30 C,D). What we observed here strikingly mirrors these results by showing that the selective amplification of informative speech is restricted to tREM but disappears in pREM, with a selective suppression of informative speech during EMs (Figure 30 B,E). **Despite the drastic physiological differences between NREM and REM sleep, these results provide a surprisingly coherent picture of the relationship between sleep depth and the selective processing of informative signals**.

Here, we hypothesized that meaningless signals would be considered as background noise and would not interfere with internal processes. Our results support this hypothesis but it remains unsettled whether Jabberwocky stories would also be suppressed during EMs if they were presented alone rather than in competition with informative stories. **It is also unknown whether the selective suppression of informative stories during EMs depends on task instructions and our results would be changed if participants were asked to focus on Jabberwocky stories instead**. Further studies are thus necessary to establish how and to what extent internal activity in REM sleep affects the sensory processing of external events.

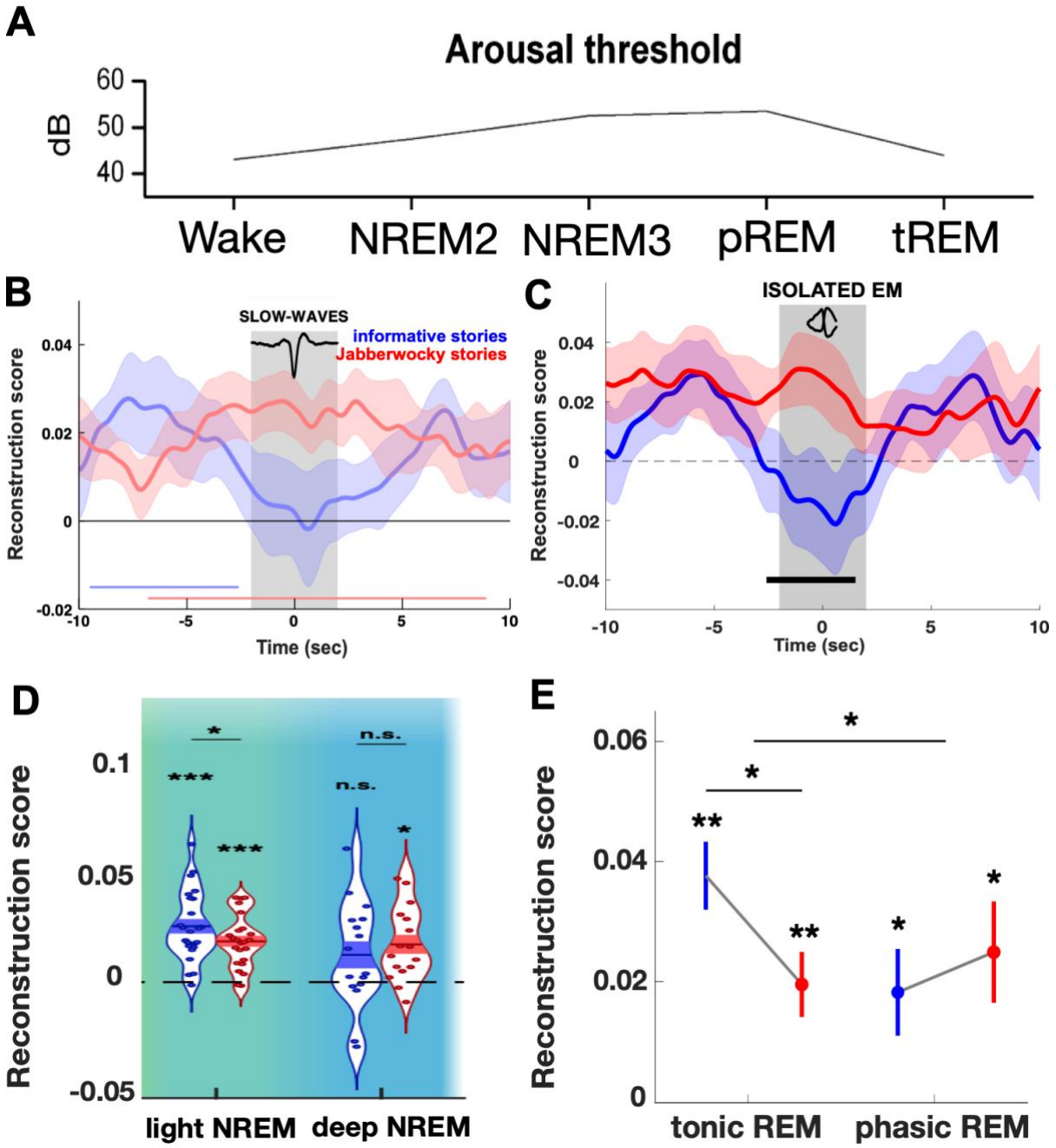


Figure 30 **Parallel between sleep depth and selective processing across NREM and REM sleep**. (**A**) Auditory arousal thresholds across sleep stages. From Ermis et al., 2010

(**B**,**C**) Time course of selective suppression of informative speech around slow waves (B) and isolated eye movements (C). B from Legendre et al., 2019

(**D**,**E**) Selective suppression of informative speech across NREM sleep (D) and REM sleep (E). D from (Legendre et al., 2019). Mean and SEM of reconstruction scores across participants are depicted. Stars show significant difference against 0 and interactions across story types and vigilance states (***: P<0.001, **: P<0.01, *: P<0.05).

4.4.3 Differential intra-trial dynamics between NREM and REM sleep

Relying on continuous stimulation, we could also test whether selective processing is sustained, transient or delayed during REM sleep. We previously observed that informative speech is preferentially processed in the first half of trials but tends to be conversely suppressed in the second half during deep NREM sleep (Legendre et al., 2019; Figure 31 A,C). For pREM, informative speech tends to be suppressed during the first half of trials but conversely amplified in the second half of trials (Figure 31 B,D). **These results extend the parallel between NREM sleep and REM sleep, yet with an exactly inverted pattern of intra-trial dynamics**.

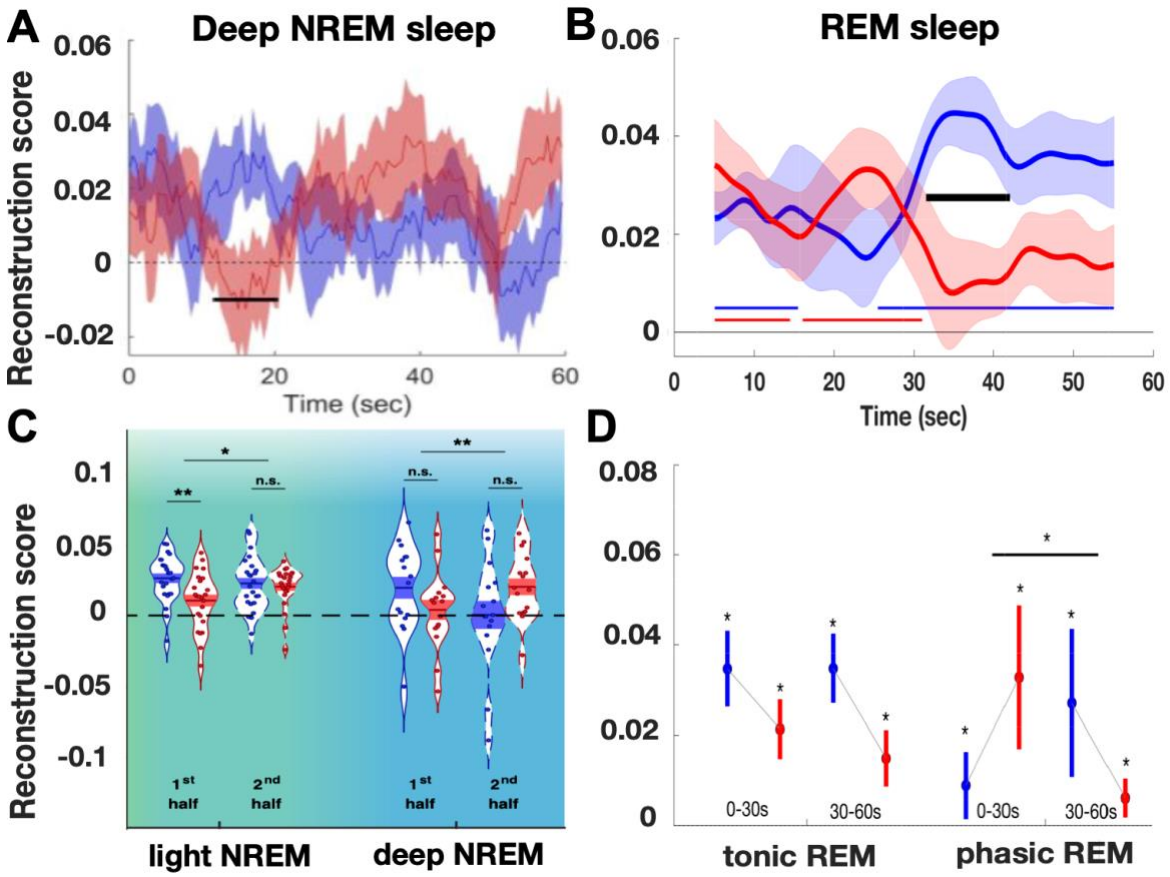


Figure 31 **Inverse intra-trial dynamics across NREM and REM sleep.**
(**A,B**) Time course of selective speech processing in deep NREM sleep (A) and in REM sleep (B). A is adapted from (Legendre et al., 2019)
(**C**,**D**) Comparison of intra-trial dynamics according to sleep depth in NREM sleep (C) and REM sleep (D). C is adapted from (Legendre et al., 2019). Mean and SEM are depicted. Stars show significant difference against 0 and interactions across story types and vigilance states (*: P<0.05).

To explain the selective suppression of informative speech in the second part of trials in deep NREM sleep, it has been proposed that sensory processing in the first half of trials would lead to slow wave activity that in return would selectively gate informative speech (Legendre et al., 2019). During REM sleep, **attentional resources could be up-taken by dreaming activity in the first half of trials but progressively dedicated to sensory processing in the second half of trials**.

Another explanation takes into account the differences in neuromodulatory context during NREM and REM sleep. The noradrenergic system is preferentially active during NREM sleep and is involved with the alerting system and the detection of salient novel information (Lee & Dan, 2012; Posner & Rothbart, 2018). Thus, selective processing of informative speech would be favored the at the onset of trials during NREM sleep. Noradrenergic bursts are also present in the transition from down states to up-states of slow waves and could take part in the regain of processing following slow waves (Sara & Bouret, 2012; Legendre et al., 2019). **Conversely, the cholinergic system is preferentially active during REM sleep and is involved with the orienting response and attentional shifts** (Jasper & Tessier, 1971; Siegel, 2004; Posner & Rothbart, 2018). Thus, a delay in selective processing could correspond to the time necessary for attentional resources to be reallocated over the course of the trial. Fast modulations of the cholinergic system have been also associated with EMs (Lee & Dan, 2012; Spreng et al., 1968a). Further works are necessary to elucidate the role of neuromodulation in selective processing across vigilance states.

4.4.4 Conclusion

Overall, this study highlights the flexibility of stimulus selection during REM sleep. The fact that informative stimuli are selectively suppressed during EMs suggests the existence of an informational gating mechanism during REM sleep. Our results provide further support for a distinction between pREM and tREM based on the selective gating of informative stimuli. They additionally provide a coherent picture of sensory gating during sleep. **Despite relying on different mechanisms, sleep depth was found to be associated with the selective suppression of informative signals in both NREM and REM sleep and this effect was associated with their micro-physiological hallmarks, respectively slow waves in NREM sleep and EMs in REM sleep**. Extension of this paradigm to situations where internal activity can be reported (e.g., mind-wandering or using a serial awakening paradigm to probe dreaming activity (Siclari et al., 2013)) would allow to investigate to which extent internally-generated conscious contents is associated with the selective gating of sensory information.

5 STUDY 3 - INFORMATION INTEGRATION ACROSS SLOW WAVES

Hypothesis:

Sensory integration can be maintained across slow waves when the task is automatized

Related work:

The role of slow waves in the integration of sensory information during sleep (Supervision, Master thesis, Dual Master (85/100))

From “Another Puzzle-Picture” (Porter, 1954)

5.1 Introduction

5.1.1 Sensory processing during deep sleep

Deep NREM sleep is characterized by a lack of response to external events. While it was first hypothetized that sensory information was blocked at the thalamic level during deep NREM sleep, a substantial body of evidence now show that incoming stimuli are processed at the cortical level (see Andrillon & Kouider, 2020 for a review). **Yet, cortical recordings revealed that neural responses, even in primary cortices, are altered during deep NREM sleep** (Issa & Wang, 2011). Indeed, a reduced sensitivity to weaker stimuli was found, suggesting that the gain in auditory processing is reduced. Moreover, stimuli outside the receptive field led to weaker neuronal suppression and an enhanced functional connectivity among neurons from the primary cortex suggests that the precision of cortical representations in the primary auditory cortex is also impaired (Issa & Wang, 2011; Issa & Wang, 2013).

Auditory stimulation during NREM sleep typically elicit an early activation of primary sensory areas, called up-state, followed by a large modality-unspecific negativity called down-state (Halász, 2016). **These activations reflect slow-wave patterns and correlate with the gating of high-level sensory processing** (Andrillon et al., 2016). This suggests that slow waves are involved in the suppression of high-level sensory processes. Yet, for items that were already trained whilst being awake, neural markers of semantic categorization were preserved even in deep sleep. This suggests that limits on complex sensory processing during deep sleep might result from the disruption of executive functions rather than sensory processes *per se*.

Slow waves are maximal over frontal regions (Massimini et al., 2004) which support executive control (Koechlin & Summerfield, 2007). **The connectivity between frontal regions and sensory areas is disrupted during sleep** (Massimini et al., 2005; Figure 32A)**. This could prevent executive functions to support the selective response to novel sensory information**. Using transcranial magnetic stimulation, the propagation of activity from frontal regions to other brain regions was studied in wakefulness and during NREM sleep. During NREM sleep, activity in frontal regions did not transfer to other brain regions, characterizing a breakdown in functional integration of the brain (Massimini et al., 2005). This loss of information was additionally reflected in the reset of the phase of high-frequency oscillations, suggesting that the transfer of information in space and time is abolished during NREM sleep (Pigorini et al., 2015; Figure 32B)

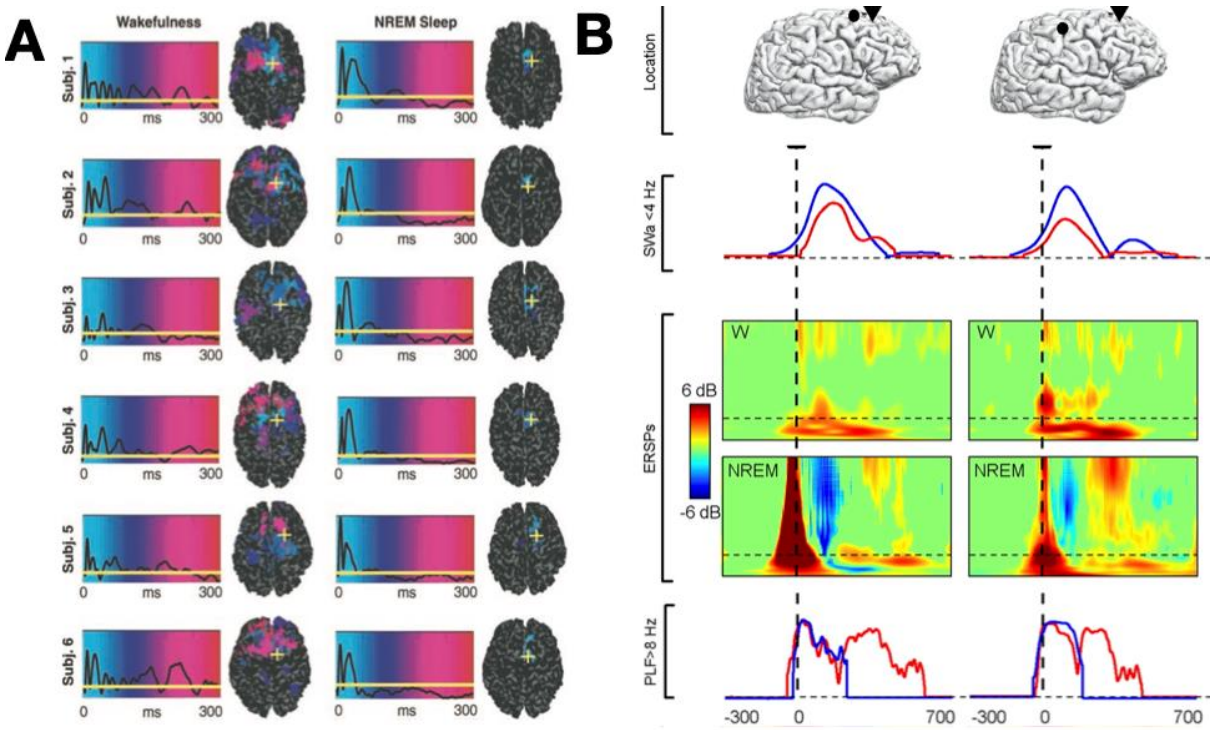


Figure 32 **Breakdown of functional activity during NREM sleep**.

A) Propagation of evoked activity by Transcranial Magnetic Stimulation. Slow wave is widespread during wakefulness but limited to the region of stimulation during deep sleep, demonstrating that the functional connectivity is impaired during deep sleep. From Massimini et al., 2005

(**B**) The consequence of such disruption is examplified by the loss of phase information for oscillations above 8 Hz in NREM sleep (blue) as compared to wakefulness (red). SWa : slow-wave activity, ERSPs: event-related spectral dynamics, PLF : phase locking factor. From Pigorini et al., 2015

5.1.2 Probing information integration during NREM sleep

This action of slow waves has been linked to the decline of consciousness during deep sleep (Tononi & Massimini, 2008). Indeed, the breakdown of connectivity induced by slow waves is coherent with leading theories of consciousness that consider either the broadcasting of information or the integration of information across cortical regions as a core feature of consciousness (Baars, 1993; Dehaene, 2014; Tononi et al., 2016). **Accordingly, neural indexes show a reduction of the level of consciousness during NREM sleep until reaching levels similar as vegetative states during deep NREM** (Casali et al., 2013; Schartner et al., 2017). To test whether sensory information is integrated, or conversely, reset across slow waves, we will apply

to sleep a protocol that has been used to probe sensory awareness during wakefulness (Gutschalk et al., 2008). In this paradigm, participants are asked to detect a tone occuring regularly, referred to as the target, among other randomly presented tones, referred to as the masker (Figure 33A). **In the original study, the detection of the target was associated with a neural signature recorded in magnetoencephalography** (Figure 33B, Targets only). When the target was played simultaneously with the masker, such signature was nevertheless reduced (Figure 33B, un-cued targets). Because tones in the masker are similar to the target tone and thus compete for attentional resources with the target, this procedure is called informational masking (Gutschalk & Dykstra, 2014). Importantly, when a cue consisting in two target tones was presented before the presentation without masker, the neural signature of auditory detection was enhanced as compared to uncued targets, demonstrating that the cue facilitated the detection of the target among the maskers (Figure 33B, cued targets).

We will adapt this paradigm to probe whether the auditory cue is integrated in NREM sleep, and more specifically across slow waves, while relying on EEG recordings. To do so, we will first shorten the trials to match the duration of a slow wave. The cue will be presented during the first up state of a slow wave, while the target and the masker will be presented during the following down states and up states of the slow wave**. To do so, we will detect in real-time the occurrence of slow waves using a brain-computer interface and present stimuli using a closed-loop stimulation procedure.**

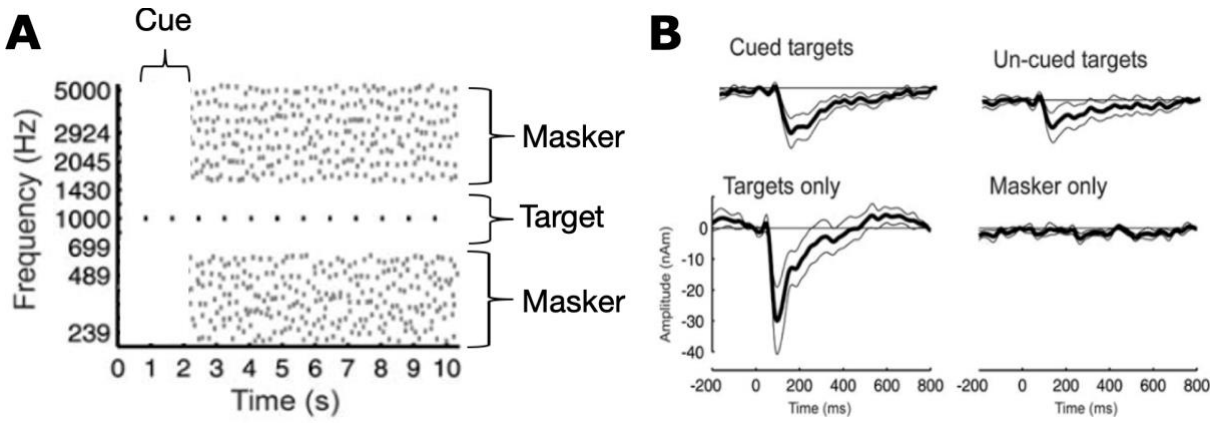


Figure 33 **Informational masking paradigm**.
(**A**) The target sound was regularly occuring among competing sounds from different frequencies. (**B**) Differential neural responses locked to target presentation reveal differential target processing across conditions. Cued targets are preferentially detected compared to uncued targets. From (Gutschalk et al., 2008)

5.1.3 Predictions on sensory integration during slow waves

Stimulus presentation will depend on the detection of the phase of slow waves. Additionally, the duration of the cue and the target with the masker will be adapted according to the period of slow waves. Closed-loop auditory procedures targeting slow-wave activity during sleep have been used to probe the function of slow waves in memory consolidation and encoding of sensory information during sleep (Ngo et al., 2013; Cox et al., 2014; Papalambros et al., 2017). **Yet, it has not been used to probe the impact of slow waves on sensory integration.**

A first prediction is that sensory encoding will depend on the phase of the slow waves. Indeed, down states are associated with neuronal silencing and thus could prevent sensory processing. Conversely, up states are associated with a regain of neuronal activity that could support stimulus processing (Steriade et al., 1993; Ode et al., 2017; Figure 34). **A second prediction is that down states might disrupt the integration of sensory information**. To test this hypothesis, a cue will be presented during an up-state and we will compute neural signatures of target detection in down states and up states.

Contrary to Gustschalk and colleagues (2018), two types of cues will be used (Gutschalk et al., 2008). The first type of cue, referred to as valid, is in the same frequency as the target in Gustchalk and colleagues (2018). **Thus, we predict that valid cues will facilitate target detection**. The other type of cue, referred to as invalid, is in a different frequency than the target. We predict that invalid cues will not help target detection. Using two types of cues ensures that the detection of the target is facilitated by the information carried by the cue rather than its mere presence. The task will be first performed in wakefulness during which behavioral response can be collected. Then, stimuli will be continuously played during sleep, and synchronized with slow waves in deep sleep.

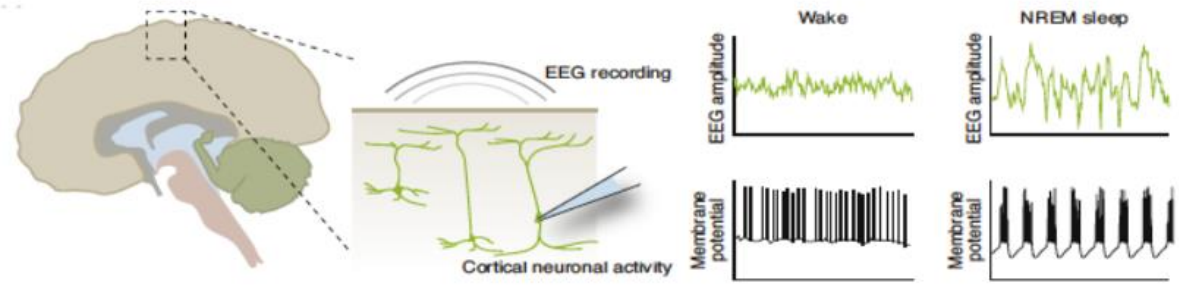


Figure 34 **Cortical activity during slow-waves**. EEG activity in deep NREM sleep reflects the bistable neuronal firing mode of synchronized cortical activity.

5.2 Methods

5.2.1 Procedure

Fourteen participants (8 Females, age 18-35 years; mean +- SD, 24.5 +/- 5.1) participated in the *Wake* study. **Twenty-three** (15 Females, age 18-35 years; 24.4 +/- 3.6) **participated in the *Sleep* study**. For the sleep study, participants matched the standards of the general population (<16 in Epworth Scale, no extreme chronotypes according to the Morningness-Eveningness questionnaire). During 5-7 days prior to the recording session, participants were asked to follow a regular sleep schedule, which was monitored using actigraphy (Fitbit Charge HR) and a sleep diary. They were additionally deprived from stimulants (e.g., caffeine) the day of experiment.

To design stimuli, tone pips were generated at varying frequencies equally spaced on a logarithmic scale between 239 and 2445 Hz (*Wake* study) or 239 and 5000 Hz (*Sleep* study) (Gutschalk et al., 2008). Tones lasted 50ms and were sampled at 44100 Hz. **Trials were composed of two parts: a cueing period and a 1s-masking period**. During the cueing period, a tone was selected among 4 possible frequencies (in *italic* for the Wake study, in **bold** for the *Sleep* study: 239, 286, 409, ***489***, 585, *699*, **836**, *1000*, 1196, ***1430***, 1710, 2015, **2445**, 2924, 3497, 4181, 5000) and occurred regularly with a constant inter-stimulus interval (ISI). During the masker period, a random masker was generated by playing tones at the other masker tones spaced with a random jitter (uniformly distributed between 25% and 175% of the ISI). The frequency bands surrounding the target frequency were excluded from the masker to facilitate the detection of the target.

The target tone was present in half of the trials (Present, +) and absent in the remaining half (Absent, -). The target tones presented during the masker period could be either identical to the target tones presented in the cue tones (Valid) or different (Invalid). This resulted in 4 different conditions: Valid+, Valid-, Invalid+ and Invalid- (Figure 35, Bottom right). During sleep, when stimuli were presented upon detection of a slow wave, the duration of the cue and the masker period was adapted to match the period of slow waves. The duration of the cue was defined as half of a slow-wave period and the masker a slow-wave period. Otherwise, the cue lasted 500ms and the masker 1s across wakefulness and sleep. Participants reported the detection of the target stream during the masker period with a right-button press and its absence by a left-hand button press, regardless of whether the target was the same as the tonality as the cue. Trials were separated by a uniformly distributed inter-trial interval (ITI) (3 to 4.5s).

Experiment 1 – Wake . The paradigm was divided into three blocks, which were composed of a training phase (4 minutes) and a test phase (8 minutes; Figure 35, Top). For each block, a different ISI was tested (50 ms, 100 ms or 150 ms). Order of blocks was randomized across participants. *Experiment 2 – Sleep* . Participants arrived at the sleep laboratory at 10pm. From 10pm30-11pm (Wake phase), they were asked to perform the same target tone detection task. The ISI was fixed to 50ms and the paradigm was composed of 4 blocks lasting 6 minutes each. Then, participants were allowed to fall asleep in a bed and the stimuli were continuously played for approximately 3.5 to 4 hours (11pm30-3am/3am30; Sleep phase). Stimulus level was adapted to participant's sleep (45-50dB). Additionally, white noise was played during the ITIs to preserve the same level of auditory stimulation throughout the night and reduce awakenings.

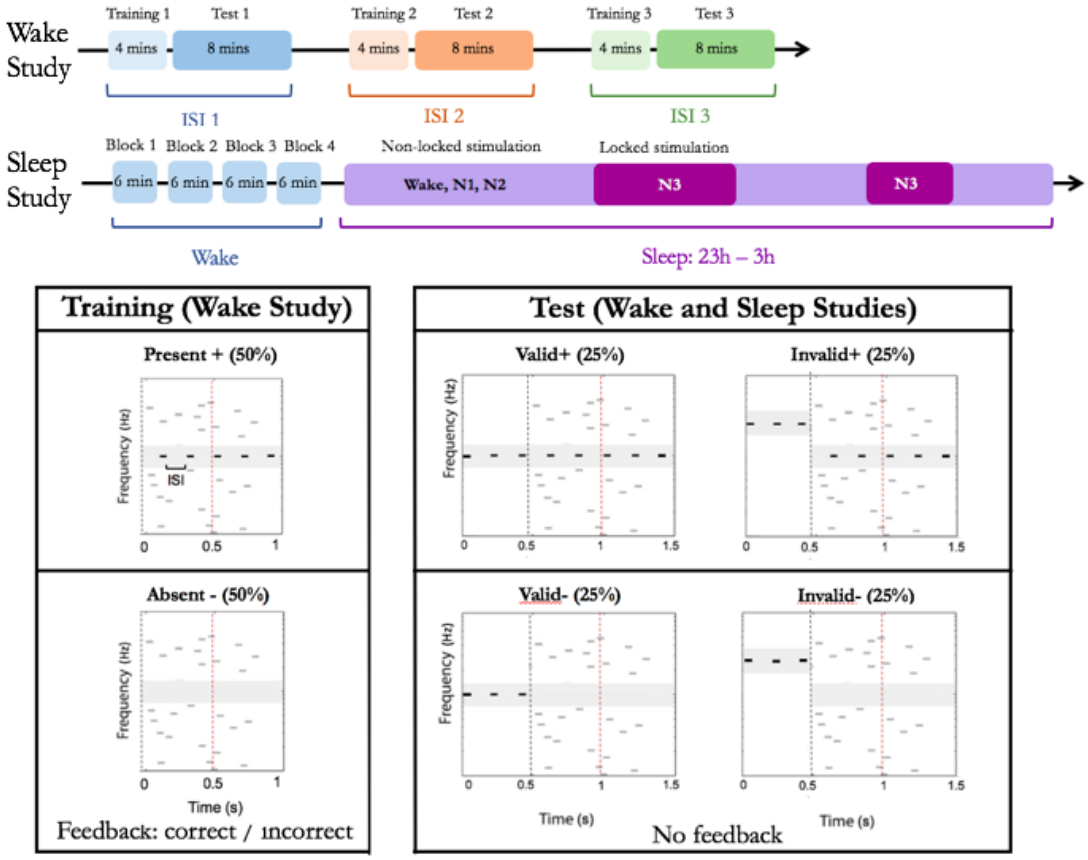


Figure 35 **Experimental paradigm for the Wake study (n=14) and the Sleep study (n=23). Top.** Schematic representation of the *Wake* and *Sleep* experimental paradigms for a single participant. **Bottom.** Schematic representation of sample auditory stimuli played in training and test blocks, respectively. In training blocks (only present in *Wake* study), 1s-long stimuli composed of masker tones alone (50% of trials) or masker and target tones (50% of trials) were presented and participants received a feedback after behavioral response. In test blocks of the *Wake* study and the *Sleep* study, a cue was presented prior to the masker that either contained a target (+) or not (-). Cue and targets tones were either the same (Valid) or different (Invalid).

5.2.2 EEG recordings

For the *Wake* study, electroencephalography (EEG) signal was recorded at 2048Hz using a BioSemi AcitveTwo System (64 channels, BioSemi V.O.F., Amsterdam, Netherlands). For the *Sleep* study, the EEG was sampled at 500Hz and recorded with an Electrical Geodesic Inc system (64 channels). An impedance of below 50mV was ensured in each electrode prior to EEG data collection. **EEG signals were referenced to the averaged mastoid electrodes and down-sampled to 256Hz in the *Wake* study and to 200Hz in the *Sleep* study**. In the *Sleep* study, EOG and chin EMG were additionally recorded.

Sleep stages were scored online and confirmed offline by two trained scorers (IEA and MK) using the FASST toolbox (Leclercq et al., 2011). Sleep stages were assessed based on EEG and EOG patterns according to established rules from the American Academy of Sleep (AASM) Scoring Manual (Iber, 2007). In addition, slow waves were detected in real time.

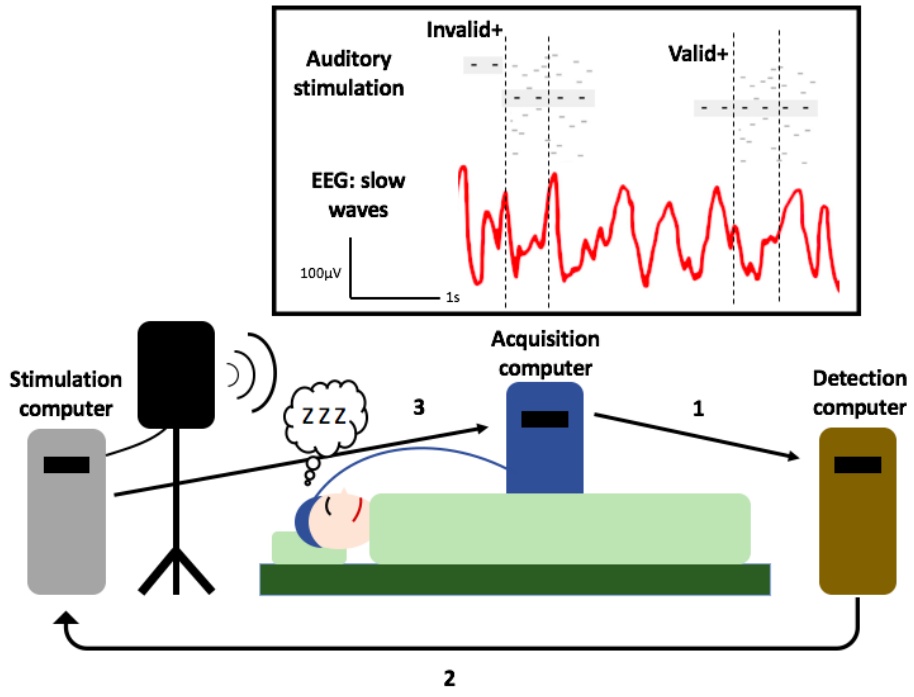


Figure 36 **Closed-loop stimulation system for the *Sleep* Experiment**. Activity at 200Hz is sent to the *detection computer* and accurate timing is ensured with Fieldtrip toolbox (Oostenveld et al., 2011) (1). The algorithm detects in real time the presence of slow waves and sends a signal to the *stimulation computer* to trigger the auditory stimulation (2). The *stimulation computer* sends a Digital Input Signal (DIN) to the *acquisition computer* to align the brain recording with the auditory stimulation (3).

To do so, the EEG signal was down-sampled to 200Hz and lowpass-filtered at 5Hz. At each time-point, the local minima and maxima of the filtered signal was detected in electrode Fz. If the following conditions were met, a slow wave was detected: 1) local maxima were above 20μV and local minima were below -20μV, 2) the difference between them was more than 75μV, 3) they were separated by 250-750ms and 4) the distance from the first zero-crossing to the next was also between 250 and 750ms. **Furthermore, a phase-locked loop (PLL) adapted a fit to the EEG signal in real-time to predict the down- to up-phase transition (zero-crossing) of the next slow wave and its period** (Santostasi et al., 2016). The cue period was locked to the first up-state of the slow wave and its duration was adapted to fit half of the period of the slow wave, while the masker period was played during the down phase and consecutive up-phase of the slow wave (Figure 36).

5.2.3 Analysis

All behavioral data was analyzed using custom-made MATLAB code (Mathworks, Inc.). To assess listener's ability to detect the occurrence of target tone sequences within the masker, we computed their *performance* for each condition, i.e. the number of correct responses over the total number of trials. For the *Wake* study, participants whose total performance across all conditions was not significantly above chance level were not included in the data analysis (7/14). The *Wake* study was aimed at assessing the best parameters to apply for the *Sleep* study. These parameters were optimized for the *Sleep* study and all participants were included. **Furthermore, we computed the detection sensitivity as measured by the *d'* index** (Creelman & Macmillan, 2005). The *d'* index takes into account participants' detection biases in favor of the detection of the presence or absence of target tones. Consequently, a significant deviation of *d'* from 0 is interpreted as the listeners' ability to discriminate between two conditions. *d'* was computed for conditions for Valid and Invalid trials separately as follows:

$$d'_{Valid} = z(Hit_{Valid}) - z(FA_{Valid})$$
$$d'_{Invalid} = z(Hit_{Invalid}) - z(FA_{Invalid})$$

z(x) is the z-score for proportion x. Hit(Valid) represents the proportion of correctly detected target tones in the Valid condition. Hit(Invalid) represents the proportion of correctly detected target tones in the Invalid condition. FA(Valid) and FA(Invalid) corresponds to the proportion of incorrect responses in Valid and Invalid conditions respectively.

EEG data was preprocessed using EEGLAB and Fieldtrip toolboxes and custom-made code in MATLAB (Mathworks, Inc.) (Delorme & Makeig, 2004; Oostenveld et al., 2011). Noisy channels were detected based on visual inspection of electrodes' traces. We first computed the standard deviations (SD) of all channels. To remove artefactual channels, channels with SD higher than the average SD across all channels plus 3 standard deviations across all channels were first identified and interpolated via triangulation using neighboring channels. Interpolated EEG data from ***Wake*** study and from the wake phase of ***Sleep*** study were high-pass filtered at 1Hz, low-pass filtered at 45Hz and re-referenced to averaged mastoid electrodes. For each trial, we isolated the EEG signal corresponding to the second where the masker period was playing. The time-course of the response over Cz was computed for each trial and baseline corrected using pre-stimulus onset activity (-0.5 to 0s). Obtained traces were averaged for each condition across participants. **The power spectrum over Cz for each trial was computed on the masker period using the fast-Fourier transform**. Obtained power spectrums were averaged for each condition across participants.

We used non-parametric (Wilcoxon signed-rank and rank-sum tests) tests to assess significant results when comparing performance and sensitivity (d'). Bonferroni test was used to correct for multiple comparison. Effect sizes for Wilcoxon signed-rank test were computed using the formula: $r= Z/\sqrt{n}$, where z is the z-stats for non-parametric tests and n the number of data-points. To investigate the effect of lists on performance score, repeated-measure ANOVA were performed with participant as a random factor. Bayes Factor was used to interpret non-significant results using the bayesFactor Matlab package (Krekelberg, 2019). Weak evidence for the null hypothesis corresponds to Bayes Factor between 1 and 3 and significant evidence above 3 (Kass & Raftery, 1995). Finally, to compare the effect sizes of the power spectrum differences between Valid+ and Invalid+ conditions for each channel, we used also the Wilcoxon signed-rank test.

5.3 Results

5.3.1 Behavioural results

We first computed performance during Training to check whether subjects were able to detect the presence of a target during the masking period in absence of a cue. **The sensitivity for all ISIs (50ms,100ms and 150ms) was not significantly above 0** ($t(22)= 0.11$, $p = 0.91$, for the main effect of ISI, Bayes Factor: 2.78, 2.23, 2.93 for ISI=50ms, 100ms and 150ms, respectively; Figure 37A). This indicates that without a cue and despite the presence of feedback following each response, the informational mask prevented subjects from detecting the presence or absence of the target within 1s-long stimulation. Moreover, this pattern was found for all ISIs showing that the frequency of the target did not affect detection.

We then tested whether the addition of a cue during the Test phases facilitated the detection of the presence or absence of the target. **Participants' sensitivity indexes (d') were modulated by the validity of the cue** ($t(44) = 2.90$, $p < 0.01$, main effect of validity of cue; Figure 37B). This shows that the cue improves target detection. We also varied the ISI to investigate the optimal parameters for the informational masking paradigm. No main effect or interaction of the selected duration of ISI was found, but targets tended to be masked more efficiently with shorter ISIs.

We thus fixed the ISI at 50ms for the *Sleep* study, allowing to raise the number of target tones during the 500ms-long cue up to 5 (instead of 3 in the *Wake* study). **With this novel paradigm, we reproduced our results during wakefulness showing that sensitivity was modulated by the validity of the cue** ($r=0.89$, $p<0.001$; Figure 37D). Sensitivity was significantly above chance level in the Valid conditions ($r=0.89$, $p<0.001$) but not in the Invalid conditions (not-significant, Bayes factor: 3.89). This effect could be traced back to a significantly better performance when the cue was valid both when target was present and absent ($t(88)= 3.11$, $p<0.001$, main effect of cue; $t(88) = -1.63$, $p > 0.05$ no interaction between the validity of the cue and the presence or absence of the cue; Figure 37C). We conclude from these results that the presence of a cue facilitates the detection of subsequent masked target tones when the cue and the target are identical. Behavioral results were thus optimized for the *Sleep* study. In the following EEG analyses, we will focus on the wake phase of the sleep study.

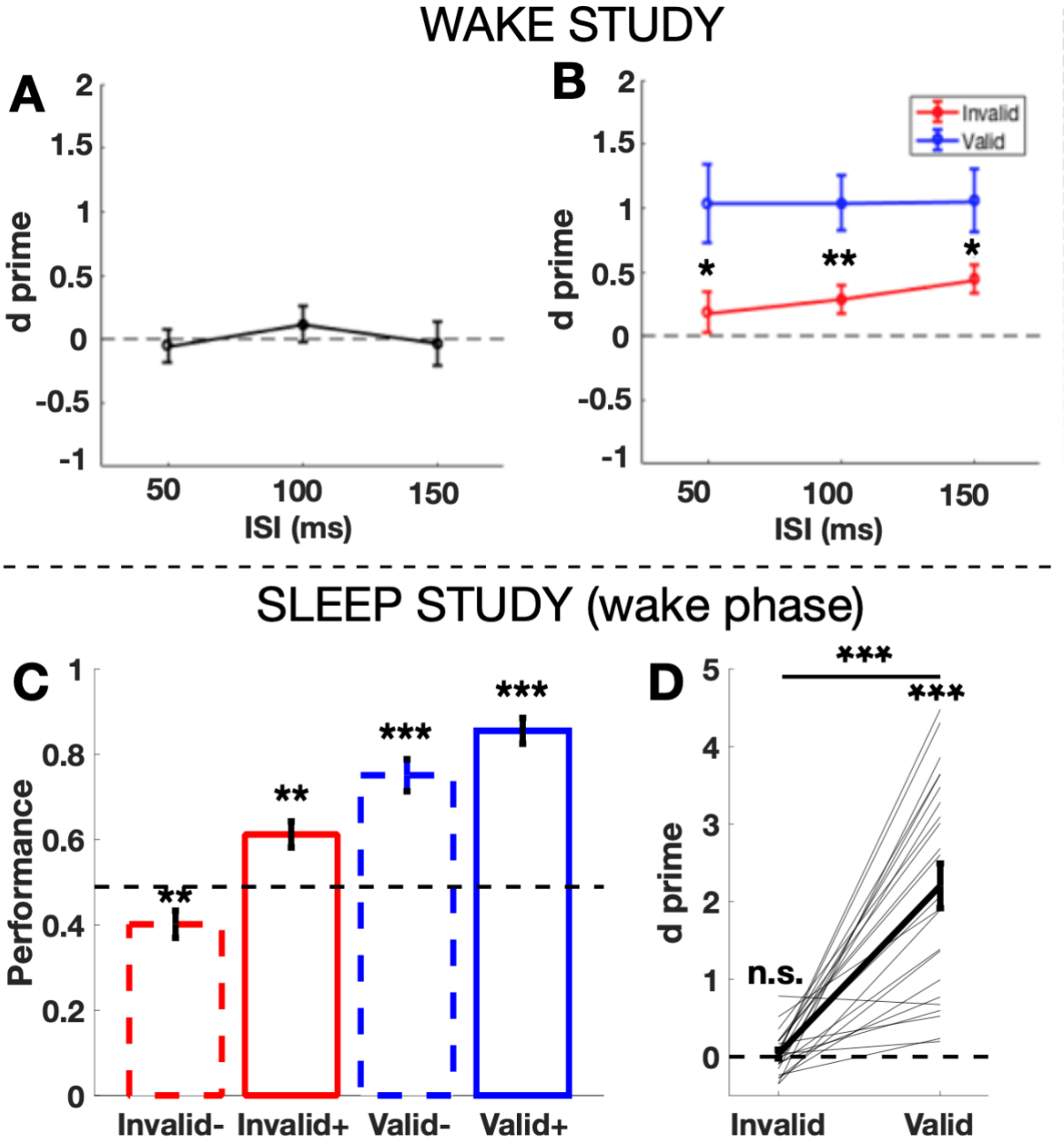


Figure 37 **Behavioral results from the wake Study and the wake phase of the sleep study**

(**A**) d' indices for Training blocks across participants for different ISIs

(**B**) Mean d' indexes for Test blocks with different ISIs for the wake study

(**C**) Performance (%) across participants for each condition during the sleep study

(**D**) d' indexes for Valid and Invalid conditions during the sleep study

In D, grey lines represent values for each participant. Across all figures, dots and error bars in bold black lines represent mean and SEM across participants. Stars show significant difference against chance level (0.5 for performance, 0 for sensitivity) and comparisons between Valid and Invalid conditions (***, $p<0.001$; **, $p<0.01$; *, $p<0.05$; n.s., not significant). Invalid is shown in red and Valid in blue. Present is shown in straight line and absent conditions in dotted line.

5.3.2 Neural markers of sensory integration

We looked for an EEG marker that indexes the detection of the target in presence of a valid cue. We first looked at the averaged activity within a trial and could identify large modulation by respectively cue onset (0s) and masker onset during wakefulness (0.5s; Figure 38A). **We did not succeed in finding significant difference across conditions when locking the electroencephalographic activity locked to the onset of the target, contrary to previously described results** (Gutschalk et al., 2008). We yet found a modulation during wakefulness around 10 Hz, i.e. at the target frequency (Figure 38D).

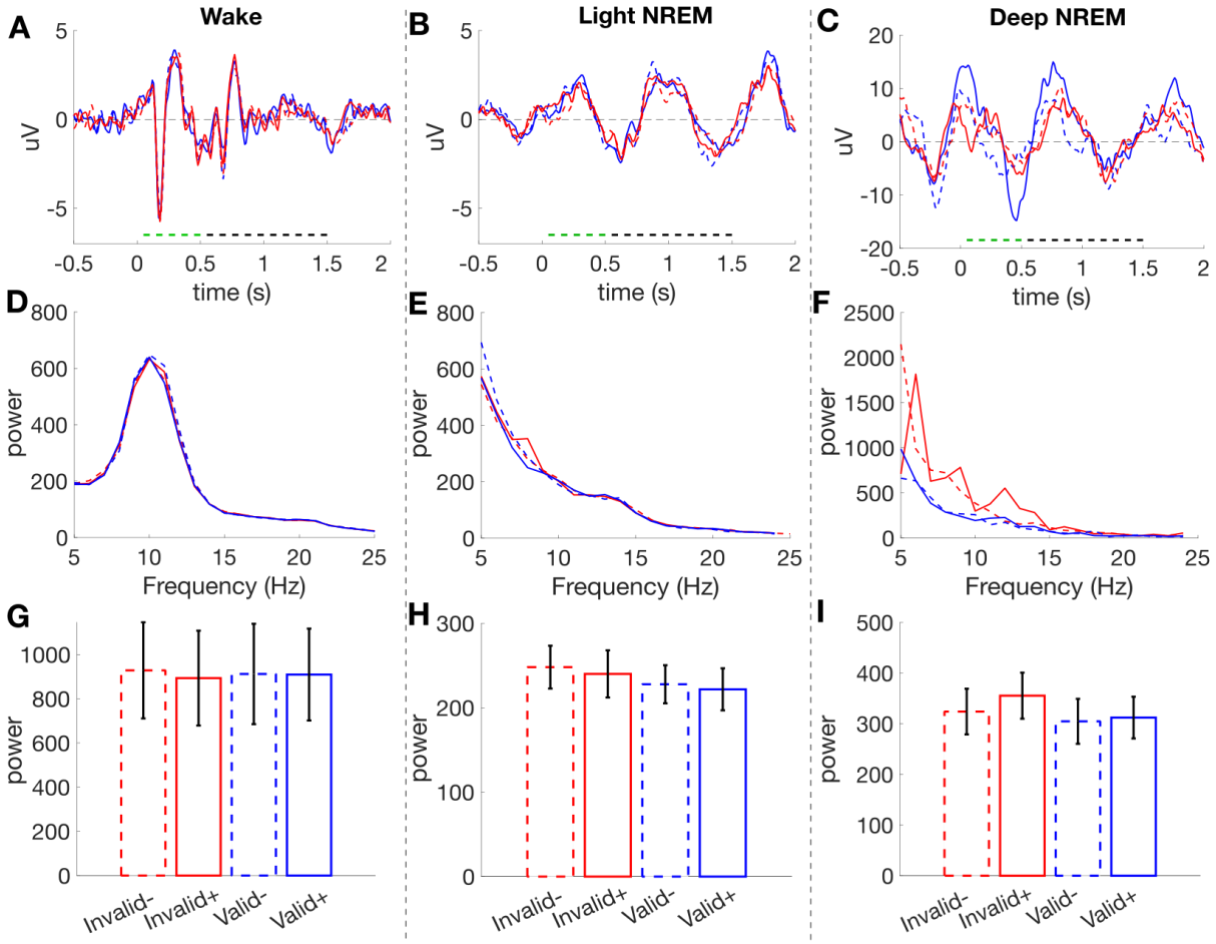


Figure 38 **Neural markers across conditions** (**A-C**) EEG trace over Cz averaged across participants for each condition (Valid+ continuous blue, Valid- dotted blue, Invalid+ continuous red, Invalid- dotted red). Lines below represent the cue (green) and target (black) tones. (**D-F**) Power spectrum over Cz during the masker period averaged across participants. (**G-I**) Power at 10Hz over Cz during the masker period across participants. Comparisons across all conditions were not significant.

Such modulation was present in all four conditions (Figure 38D). No significant difference across conditions was found in any electrodes ($p>0.05$ after correction for multiple comparisons; Figure 38G). We conducted the same analyses in light NREM sleep and deep NREM sleep (Figure 38 E,F). Yet, we did not find a significant modulation of the 10 Hz rhythm and no difference across conditions was found ($p>0.05$ after correction for multiple comparisons; Figure 38 H,I).

More sensitive decoding methods were tested but no reliable neural marker of target detection during wakefulness was identified. An alternative approach is to investigate whether some experimental conditions influence the ongoing sleep rhythm. For example, the entrainment of slow wave activity is more pronounced in response to familiar names and voices during deep sleep (Blume et al., 2018). We first detected with an offline detection algorithm the presence of slow waves up states and down states (see Methods). Yet, we did not find significant difference in the induction of slow waves patterns across the different conditions.

5.3.3 Closed-loop stimulation

As expected, participants had a majority of light and deep NREM sleep during early sleep (Table 10). Slow-wave density in slow-wave sleep was comparable to previous studies (e.g. 14±2,1 for an afternoon nap (Legendre et al., 2019). **This allowed us to play 826±55 (mean±SEM) stimulations in light NREM sleep and 808±66 in deep sleep**.

The real-time algorithm detected 779±58 slow waves. Our algorithm was furthermore successful in targeting the first up-state 0-crossing and thus present the stimulation locked to the phase of slow waves (Rayleigh test for non-uniformity of circular data: $r = 10.6$, $p<0.001$; Figure 39B). We further distinguished slow-wave predictions which were successful when the 0-crossing was followed by a down-state (116±38 per participants) from situations where predictions failed. This consists in cases where detection was followed only by an up-state (230±51) or by neither an up-state nor a down-state (432±95) (Figure 39C).

Our closed-loop stimulation procedure allowed to present 256±43 trials locked to slow waves among all these detections. The presence or absence of subsequent down states and up states could play the role of control conditions for further analyses. They would allow to distinguish the specific effect of an up state and a down state on sensory integration.

Table 10 **Sleep statistics during the early-night sleep**. Sleep duration was computed as the time spent in consolidated sleep, i.e. in N2, N3 or REM sleep. SW density was computed as the number of events divided by the number of minutes spent in deep sleep. Sleep latency was computed as the duration until the first apparition of N2 sleep stage after switching off the light. Sleep efficiency was computed as the percentage of time spent in NREM or REM sleep during the sleep phase.

	Sleep duration (min)	**Duration of N2 (min)**	**Duration of N3 (min)**	**Duration of REM (min)**	**SW density (.min-1)**	**Sleep latency (min)**	**Sleep efficiency (%)**
Mean±SEM	165±6.3	76±6.1	78±6.8	12±2.5	19±2.4	27±3.6	82±2.1

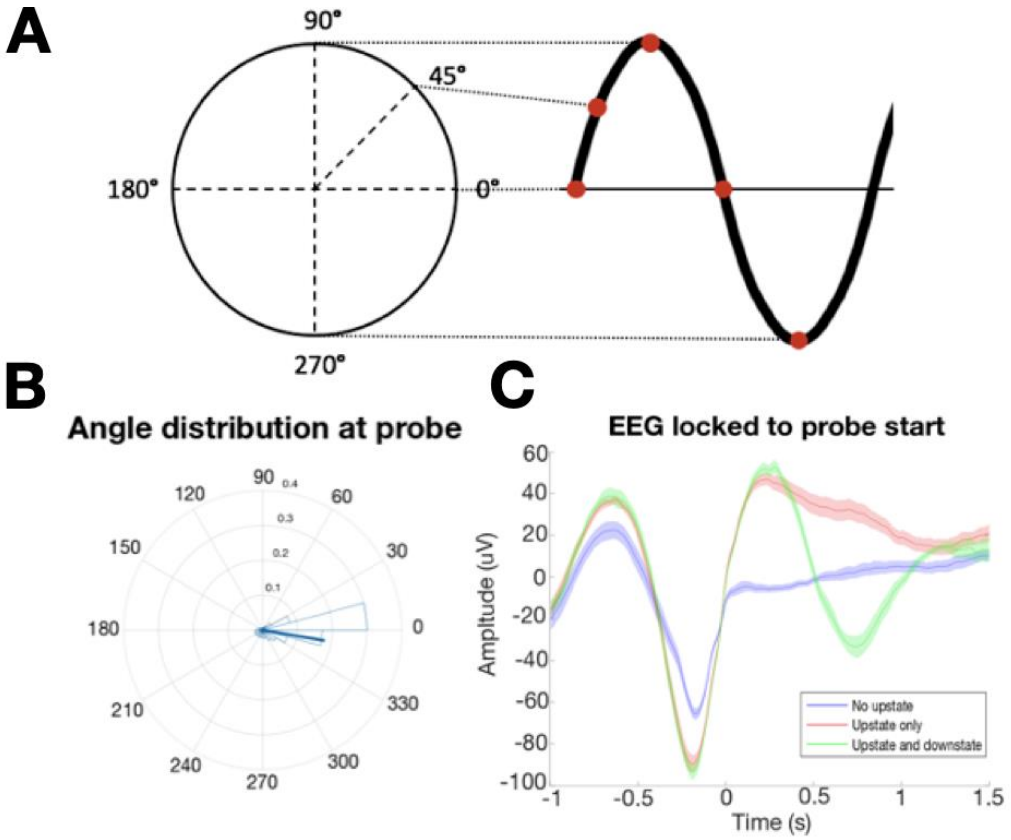


Figure 39 **Real-time stimulation coupling**.

(**A**) Schematic representation of phase angle of slow wave. 0°, first zero-crossing, 90°, peak of the up state and 270°, trough of the down state

(**B**) Polar histogram showing the distribution of the phase angle of the slow wave at electrode Fz at which auditory stimulation was initiated. The line represents the mean phase across participants.

(**C**) EEG signal at electrode Fz locked to stimulus onset. A full slow-wave could follow detection (green), an up-state without a down-state (red) or no up-state nor a down-state (blue). Mean and SEM across participants are represented as straight lines and shaded areas.

5.4 Discussion

5.4.1 Evidence for sensory integration

Participants were unable to detect the target tones in the absence of cue, as shown in the training phase of the *Wake* study. Presence of feedback informing participants about correct and incorrect detection did not improve detection. **Yet, when a cue of the same frequency as the target tone was included before the masker period, participants were able to successfully detect masked target tones**. Despite using shorter trials than Gutschalk and colleagues (1 vs 10s), we could still find a robust effect of the cue on the target detection. Our additional divergence from the Gutschalk and colleagues is the addition of an invalid cue as a control condition. This allowed to show that the facilitation by the cue was not due to an increased preparedness in the processing of incoming stimuli, but crucially relied on the informational content of the cue.

Our cueing procedure resulted in an unexpected effect: valid and invalid trials yielded different results in the absence of the target. **Invalid- trials had a performance below chance level revealing that subjects detected a target even in its absence**. Contrary to valid- trials, tones belonging to the masker were played irregularly in the same frequency as the cue in invalid- trials. This could explain why participants tended to detect target tones in invalid- trials as they could confuse the presence of irregular masker tones for the presence of the target. To our knowledge, such effect of informational masking has not previously been reported in the literature. This provides further evidence that our subjects integrate information from the cue to facilitate the subsequent detection of the presence and absence of target tones or impair such distinction when the cue is invalid.

We investigated the neural markers of target detection. First, we studied the EEG response locked to the stimulus onset. Here, we relied on a EEG rather than MEG as in Gutschalk and colleagues (2008). Additionally, shorter ISIs were used resulting in a higher density of masker tones. Finally, trials were shorter. We thus had a reduced signal-to-noise ratio in our study and we failed to observe a reliable evoked potential locked to stimulus onset or to target tones across conditions. Thus, we studied whether the spectral brain signal was modulated at the target frequency. **We found a peak at the target presentation frequency at 10Hz**. When probing the topography of these results, we noticed that differences between the Valid+ and the Invalid+ were strongest around temporal regions, which fits the localization of auditory sensory areas.

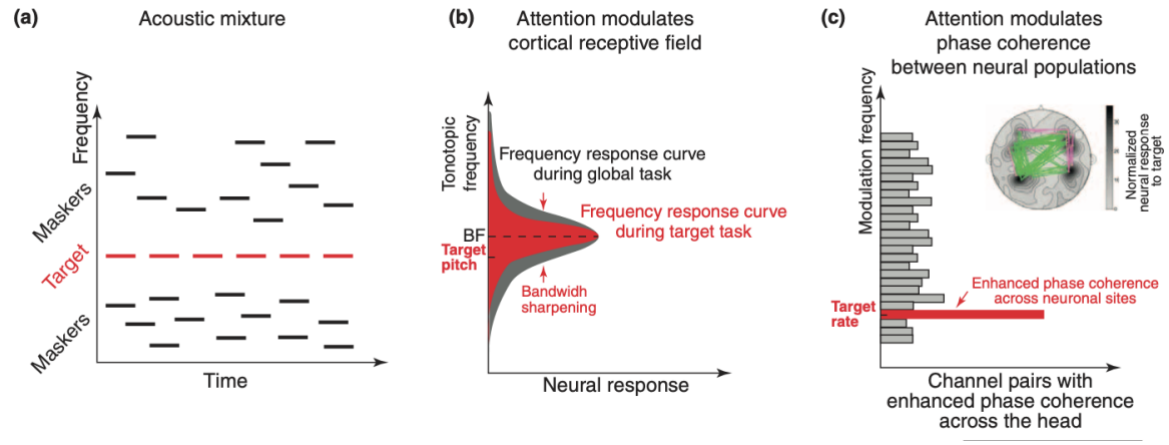


Figure 40 **Schematic representation of the influence of attention on the selective tracking of sound and its associated neural correlates**

(**A**) Schematic of the time–frequency distribution of an acoustic mixture with a regularly repeating tone sequence (target) among random tones (maskers).

(**B**) Illustration of the frequency–response curve for a single unit recorded in the primary auditory cortex of a behaving ferret. The receptive field tuned to the target frequency sharpens when the animal attends to the repeating target tone (target task, red curve) and broadens when attending to the entire sound mixture (global task, grey curve)

(**C**) Phase coherence between distinct neural populations as measured by distributed magnetoencephalography (MEG) channels recording neural activity in human subjects. The phase coherence contrasts a selective attention task (in which subjects attended to the repeating target tone) to a global attention task (in which subjects paid attention to the background maskers). Channel pairs with enhanced phase coherence are shown in green and channel pairs with reduced coherence are shown in pink. From (Shamma et al., 2011).

5.4.2 Difference of sensory processing during wakefulness and sleep

The amplitude of steady-state auditory responses has been reported to vary across vigilance states (Cohen et al., 1991). Using a similar task as ours, other markers of target detection such as phase coherence have been identified in MEG (Shamma et al., 2011; Figure 40). An increase in the coherence at the target frequency correlated with target detection. Whether this applies to EEG measures in the context of this task has not yet been studied. Furthermore, NREM sleep is characterized by an increase in the modularity of the brain network (Boly et al., 2012; Tagliazucchi et al., 2013). Thus, it might be that the connectivity between different brain regions, such the temporal areas involved in auditory processing, might be affected during sleep. How these measures are affected by sleep patterns and conditions is under investigation in our lab.

We demonstrated that we could successfully trigger stimulation locked to slow waves in NREM sleep. The brain-computer interface algorithm achieved state-of-the-art performance and demonstrated the possibility of presenting different parts of the stimuli synchronized to the slow-wave rhythm. A difference between valid and invalid conditions would count as evidence that auditory information is integrated over the down state of a slow wave, as suggested by the preserved auditory processing of non-informative speech signals across slow waves (Legendre et al., 2019).

Whether such integration relies on bottom-up processes or top-down processes has been debated (Elhilali et al., 2009). Bottom-up processes support stream segregation and would help to distinguish the target tones from the masker (Fishman et al., 2001) (Figure 41). Top-down mechanisms are conversely involved in the stream selection and would allow for the tracking of the target despite the presence of a competing masker (Elhilali et al., 2009; Shamma et al., 2011). **NREM sleep is associated with a breakdown of functional connectivity** (Massimini et al., 2005) **and hierarchical processing** (Strauss et al., 2015). **Sleep represents a case study for sensory integration as both processes might be dissociated during sleep while they are coupled during wakefulness.**

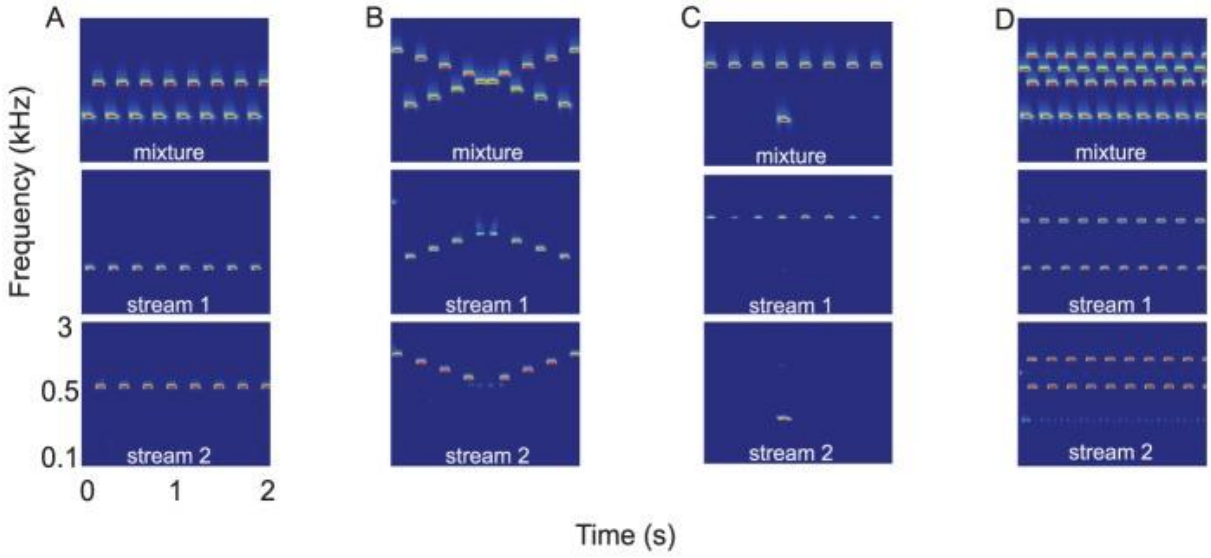


Figure 41 **Examples of bottom-up stream segregation of tone sequences in complex sound mixtures.** (**A**) The classic case of the well-separated alternating tones (top panel) becoming rapidly segregated into two streams (middle and bottom panels).
(**B**) Continuity of the streams causes the crossing alternating tone sequences (top) to bounce maintaining an upper and a lower stream (middle and bottom panels).
(**C**) Continuity also helps to maintain a stream in presence of desynchronized tones.
(**D**) Sequences of tones desynchronized by more than 40 ms (top panel) segregate into different streams despite a significant overlap (middle and bottom panels). From (Krishnan et al., 2014)

5.4.3 Extension of this paradigm

Pigorini and colleagues relied on non-invasive electrical stimulation to show that down states resulted in a reset of cortical oscillatory patterns (Pigorini et al., 2015). Whether this loss of information across slow waves can be generalized to any type of information is unknown. Visual stimulation through eyelids has also shown to robustly entrain neural activity at frequencies imposed by the stimulus during NREM sleep (Sharon & Nir, 2018). **Investigating sensory integration across different modalities and vigilance states allows to characterize whether the generalizability of the disruption of information integration during NREM sleep.**

Another interesting possibility would be to extend this question to REM sleep. As REM sleep is characterized by a regain of consciousness, it may be particularly relevant to assess whether sensory integration is altered, or conversely, preserved during REM sleep. Whether the presence of eye movement would further modulate sensory integration would allow to comparatively study the impact of slow waves in NREM sleep and eye movements in REM sleep. **Furthermore, slow waves also happen in human REM sleep** (Bernardi et al., 2019). The role of slow waves in REM sleep in the sensory gating of external stimulus remains unknown.

A third situation in which slow waves can be observed is after prolonged sleep deprivation during wakefulness (Vyazovskiy et al., 2011). **Neural silencing during slow waves causes slower reaction times and behavioral errors, a phenomenon called behavioral lapses**

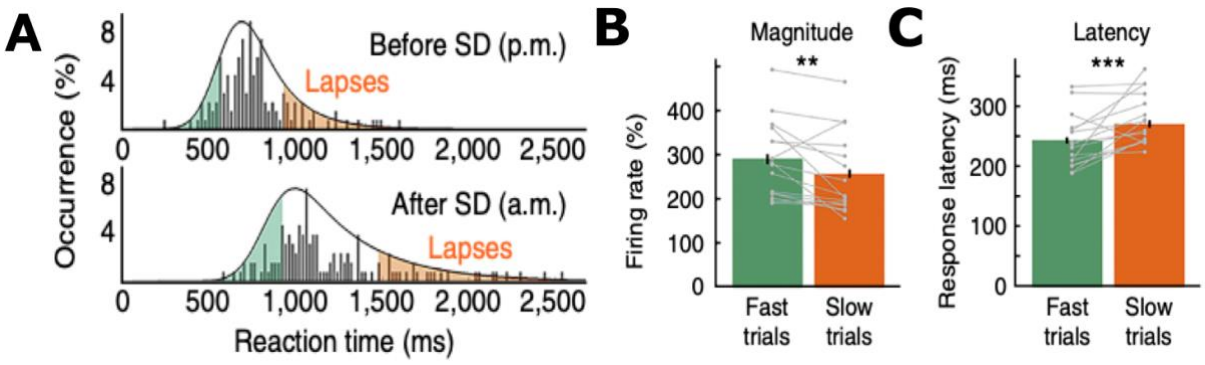


Figure 42 **Neural correlates of behavioral lapses after sleep deprivation.**
(**A**) Distribution of reaction times (RTs) before and after full-night sleep deprivation (SD)
(**B-C**) Quantification of response magnitude (B) and response latency (C), in individual responsive neurons during fast trials vs. slow trials (N=376 pictures in 142 units). (**, p<0.005, Wilcoxon signed-rank test; ***, p<0.0005, Wilcoxon signed-rank). From (Nir et al., 2017)

(Nir et al., 2017; Figure 42). Studying how sensory processes are affected by slow waves during sleep deprivation and how they affect sensory integration would allow to better understand the cognitive bases of behavioral impairments observed in sleep deprived conditions. Furthermore, the development of BCI that allow for the online detection of slow wave activity might offer a possibility to monitor in real-time the subjects' responsiveness to their sensory environment and help to prevent the drastic consequences of neural fatigue on behavior (Duffy et al., 2015).

5.4.4 Conclusion

Overall, we designed a novel paradigm probing the integration of sensory information. We coupled stimulus presentation with the detection of slow waves in real time. Neural markers of sensory processing are required to investigate to what extent sleep processes disrupt sensory information. The use of BCI to adapt sensory stimulation in real time represents a promising line of research to probe neural process that affect the cognitive functions involved in the levels of consciousness and variations of vigilance.

6 GENERAL DISCUSSION

In this section, we will discuss the general theoretical and methodological insights of our studies. In a first part, I will interpret our results in regard of the interaction between endogenous processes and sensory processing in diverse vigilance states. In the second part, I will discuss the methodological key points developed in this thesis. Finally, I will outline the research direction that I will consider in the next years.

"Stay (dis)connected" WYNKL

Related works:

Hohwy, J. & Koroma, M. (2017). On different ways of being conscious: modes of consciousness and the predictive mind. An interview with Jakob Hohwy. *ALIUS Bulletin*, *1*, 17-23.

Fox, K. & Koroma, M. (2018). Wandering along the spectrum of spontaneous thinking: dreaming, meditation, mind-wandering, and well-being. An interview with Kieran Fox. *ALIUS Bulletin*, 2, 1-

Bayne, T., Bucci, A. & Koroma, M. (2019). How to study consciousness as a natural phenomenon. An interview with Tim Bayne. *ALIUS Bulletin,* 3, 1-9.

Matthieu Koroma (2018) An emotion regulation account of the paradox of fiction, draft

Matthieu Koroma (2019) Self-evidencing conscious experience and vicious circularity, draft

Magritte (1955) the masterpiece of the mysteries of the horizon

6.1 Insights into sleep functions

6.1.1 Sensory processing across vigilance states

Sleep is characterized by a reduced responsiveness to external events, yet we found that the sleeping brain remains responsive to sensory stimuli. By decoding the neural responses to auditory stimulation during experimental tasks, we could probe sensory processing across vigilance states. **We found overall that auditory stimuli are processed at the cortical level, are selectively processed and can lead to memory formation both during wakefulness and sleep**. These results are in line with a substantial body of evidence that the brain is not disconnected from the external world during sleep and that actually a wide range of complex cognitive processes remains functional (see Andrillon & Kouider (2020) for a review). Yet, comparing these processes during wakefulness and sleep also reveal the drastic cognitive differences between these two states.

First, the memory formed during NREM sleep was implicit, while the memory formed during wakefulness in the same task was explicit. **This result supports a view dissociating memory processes occurring during wakefulness and sleep**. While learning being awake would be efficient to rapidly encode new explicit memories based on hippocampal activity, sleep learning would necessitate the repetition of rigid associations (Henke, 2010; Figure 43). Second, we found that selective processing of external stimuli was preserved during sleep, but the dynamics of attentional allocation differed significantly across vigilance states. Selective processing was sustained during wakefulness, whilst being only transient during NREM sleep and delayed during REM sleep.

Overall, our results suggest that mental activity presents both some continuity and key differences across vigilance states. Whether mental activity during sleep is in continuity or discontinuity with wakefulness has been discussed regarding dream content (Schredl et al., 2009). A similar debate can be also discussed for vigilance. On one side, the cognitive processes supporting stimulus detection, selection and integration are still functional during sleep. On the other side, we observe lower sensitivity to external stimuli, reduced selective processing during sleep and less efficient memory encoding. **An alternative approach is to shift the focus away from vigilance states and identify the processes supporting cognitive activities at play**. This strategy has been discussed about memory and defended a dissociation of memory systems based on memory processes rather than conscious states (Henke, 2010; Figure 43).

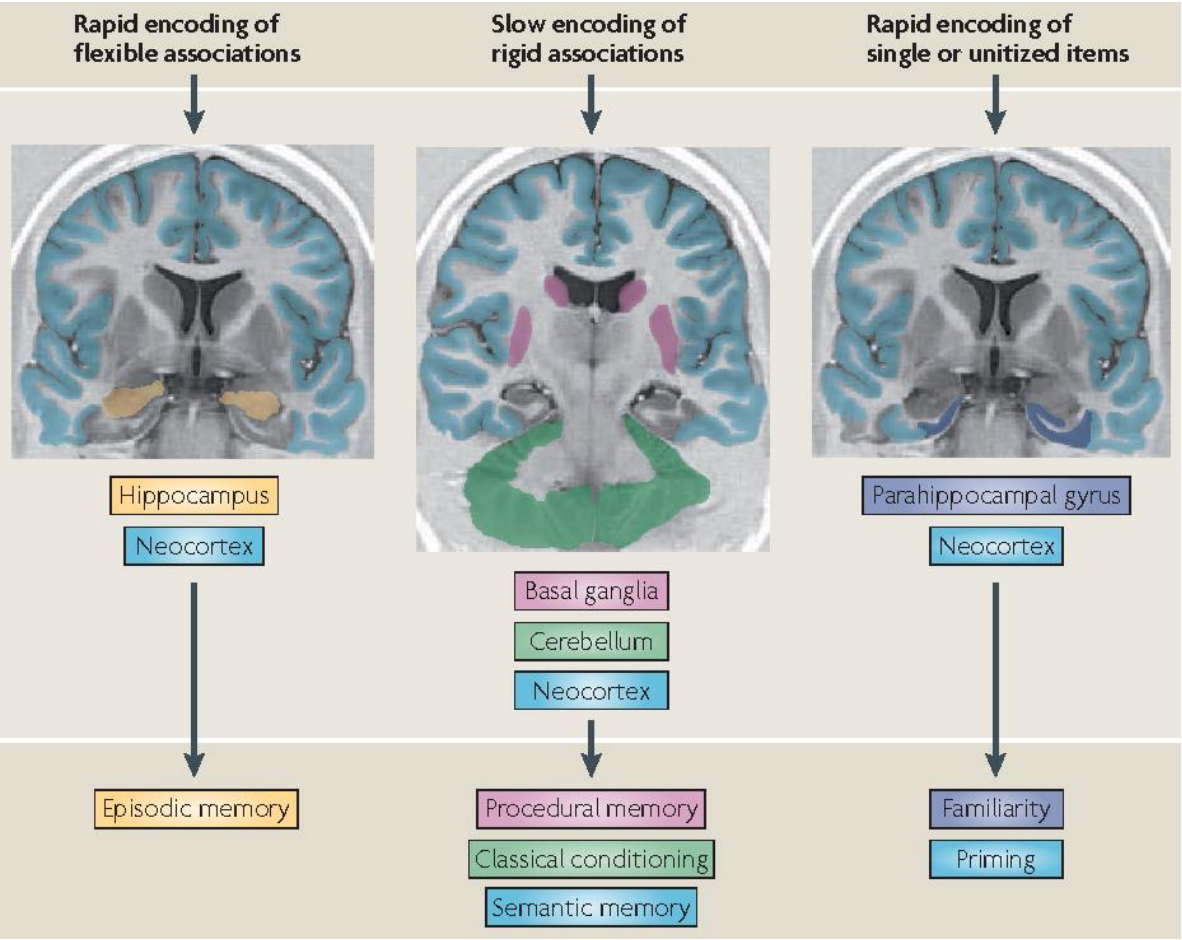


Figure 43 **A process-based division of memory systems.** The model distinguishes three basic processing modes that differ with respect to three variables: rapid versus slow encoding; associative versus single item encoding; and flexible and compositional versus rigid and unitized representation. Episodic memory refers to rapidly encoded and flexibly represented associations of any kind and relies on the hippocampus and neocortex. The slow encoding of rigid associations engages the basal ganglia, cerebellum and neocortex for classical conditioning or for the creation of new procedural or semantic memories. The rapid encoding of single or unitized items involves the parahippocampal gyrus and neocortex to afford priming and familiarity. From Henke, 2010

6.1.2 The key role of microphysiology in sensory processing

Recent results discussed the cognitive processes related to vigilance beyond the classical wake/sleep dichotomy. Dreaming during sleep has been proposed to be an intensified form of mind-wandering (Fox et al., 2013; Figure 44A). Slow-wave activity has been first identified during sleep, yet it has been involved in behavioral lapses in wakefulness and its presence explains some phenomenological features of mind-wandering (Nir et al., 2017; Andrillon et al., 2019 ; Figure 44B). Memory retrieval in wakefulness has been considered as a fast route for memory

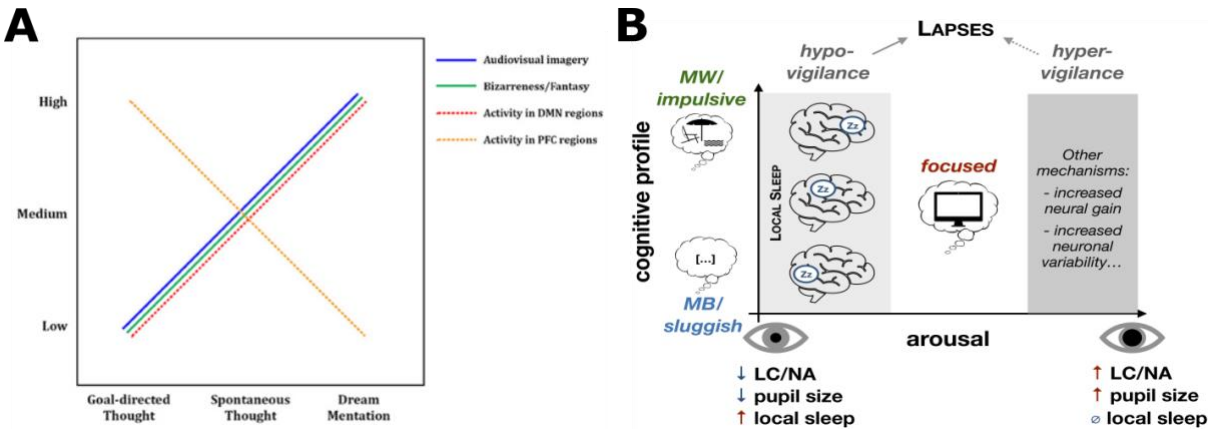


Figure 44 **Links proposed between sleep phenomena and mind wandering**. (**A**) Tentative model of dreaming as an intensified form of mind-wandering. Solid lines represent subjective, experiential elements; dashed lines represent brain activity levels as measured by regional cerebral blood flow using PET, or BOLD (blood-oxygen-level-dependent) signal using fMRI. DMN, default mode network; PFC, prefrontal cortex. From Fox et al., 2013 (**B**) Localisation of the intrusion of local sleep explaining the phenomenology of lapses. MW, mind-wandering, MB, mind-blanking, LC, locus coruleus, NA, noradrenalin. From Andrillon et al., 2019

consolidation, a process that was traditionally associated with sleep (Antony et al., 2017). The focus shifts from the macro-physiology of cerebral states defining vigilance states in favor of micro-physiological markers of cognitive processes. Accordingly, we observed that sensory processing interacted with the micro-physiological markers of cognitive activity during sleep.

We first found that memory performance was predicted by the neural responses to stimuli during NREM sleep. Memory performance at awakening was predicted by the presence of a neural oscillation at a slow-wave rhythm during sleep, in line with recent results showing the involvement of slow-wave activity in associative memory formation during NREM sleep (Züst et al., 2019; Canales-Johnson et al., 2020). Moreover, we could show that these neural responses evolved across the learning process and could reflect the reorganization of the brain network supporting the formation of associative memory.

We also provided evidence that eye movement activity correlates tightly with sensory gating during sleep. We showed beyond previous results that informative stimuli were selectively suppressed during eye movements. As eye movements are associated with dreaming activity (Hong et al., 2018), we proposed that this suppression results from a competition for attentional resources

between sensory processing and internally-generated processes. **We further observed a striking similarity between the selective suppression of informative stimuli during eye movements and slow waves** (Legendre et al., 2019). Despite relying on different mechanisms and occurring in different brain states, internally-generated processes indicated by the presence of micro-physiological markers explain part of the variations of vigilance. Vigilance and sleep processes might be viewed here in opposition, yet their daily alternation and the presence of homeostatic regulation in wake/sleep cycles suggest conversely that they are complementary processes.

6.1.3 Divisions of labour across vigilance states

Attention, by filtering incoming stimuli based their relative salience, has been proposed to be a key component in the balance between wakefulness and sleep (Kirszenblat & van Swinderen, 2015). By selecting incoming information during wake, attention builds up sleep pressure and shapes sleep consolidation processes, while in return, sleep restores attentional abilities and shapes stimulus selection during the day. Wakefulness and sleep has been proposed in this respect to host complementary processes regarding the processing of sensory information (Vyazovskiy et al., 2008). **While wakefulness allows for the sampling of the environment, as revealed in our results by sustained attentional abilities and rapid memory encoding, sleep allows for the offline reprocessing of sensory information to optimizes its encoding, resulting in our studies in lower attentional abilities to external information and reduced memory encoding** (Rasch & Born, 2013; Tononi & Cirelli, 2014; Figure 45)

We also found distinct effects on sensory processing between NREM and REM sleep. Selective processing was found more prominent in the start of stimulation during NREM sleep, while such processing was delayed for REM sleep. **The neuromodulatory context offers an interesting dissociation in NREM and REM sleep, as the noradrenergic modulation is predominant during NREM sleep while the cholinergic system is more active during REM sleep**. Early information selection and cortical encoding associated could be promoted by noradrenalin modulation during NREM sleep. Conversely, attentional shifts in information selection and information integration could be promoted by cholinergic modulation during REM sleep. The role of the alternation of NREM and REM sleep on cognitive functions, such as the formation of semantic associations, could not be directly investigated in our studies but highlights the complementarity of both states, as proposed for example by the sequential hypothesis (Giuditta et al., 1995).

Momentary changes of neuromodulation also operate at the micro-physiological level. Bursts of noradrenalin occur during the down-to-up transitions of slow waves (Sara & Bouret, 2012) and fast modulations of cholinergic activity are observed during EMs (Spreng et al., 1968). Even if these two processes would rely on fundamentally different mechanisms, our results hinted that slow waves and eye movements could have a converging function. **An intriguing possibility is that slow waves, by disrupting the integration of information across time, may favor attentional shifts across memory traces and the comprehensive sampling of memory traces during memory consolidation and synaptic downscaling. Similarly, eye movements could indicate shifts in the dream scenery allowing for the comprehensive sampling of cortical activity and the reorganization of memory traces across cortical networks**. How sensory integration is disrupted by the occurrence of slow waves and eye movements and how they support sleep functions related to memory reprocessing during sleep are two outstanding questions for sleep research highlighted by our results.

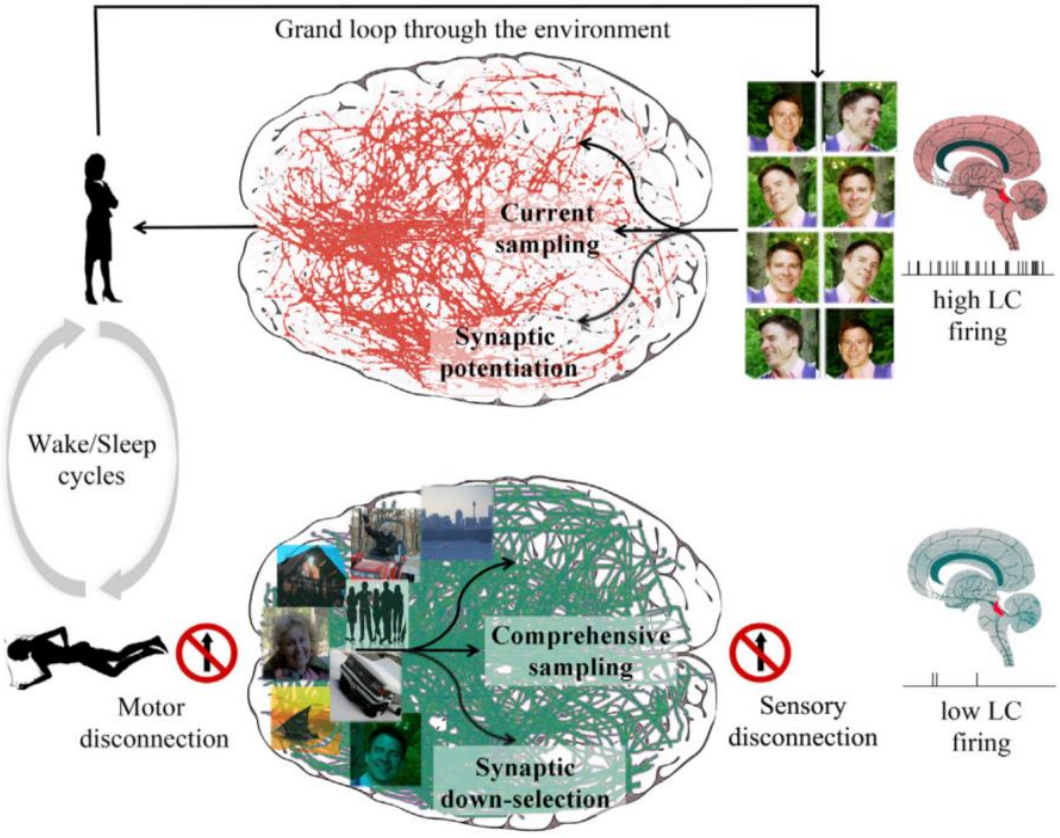


Figure 45 **Complementary roles of wakefulness and sleep in sensory processing**. During wakekefulness, the sampling of the environnement is encoded in synaptic activity. During sleep, internal representations are sampled to optimize synaptic encoding. From Tononi & Cirelli, 2014

6.2 Breaking through sleep disconnection

6.2.1 Using complex stimuli to probe vigilance

To uncover sleep internal processes, we relied on complex stimuli, involving multiple streams of information. For study 1, we showed that sleepers could effectively associate two different information, one being a characteristic sound and the other a verbal information, i.e. the Japanese translation. For study 2, we could show on the contrary that sleepers could dissociate two auditory streams and track one stream separately from the other. In study 3, a target was embedded within a masker to study how sensory integration led to stream segregation or, on the contrary, the fusion of both auditory streams. **Going beyond the encoding of simple stimuli during sleep, we could study how auditory information could be discriminated, or on the contrary, associated during sleep.**

Additionally, we studied the selectivity of sensory processing. In study 1, by performing a two alternative forced choice task at awakening, we could test for the specificity of associations formed during sleep. **In study 2, we showed that informative speech is selectively amplified or suppressed during sleep, demonstrating that the selection of information could be flexibly modulated during sleep**. In study 3, we showed that the presence or absence of a target stream could be effectively detected in an informational masker during wakefulness. Presenting sensory information in competition allows to probe the selectivity of sensory processing across vigilance states.

We finally investigated whether sensory information was integrated across time. In study 1, we explored this integration by repeating the same auditory information across sleep. **We showed that neural traces evolved with the learning process and predicted long-term memory formation during sleep.** In study 2, we showed that over a 1-minute stimulation, selective processing varied across time. In study 3, we investigated into how sensory streaming could be facilitated by the presence of a cue. These results highlight the temporal dynamics of information integration in diverse vigilance states.

6.2.2 Decoding sleep covert processes

To decode sensory processing during sleep, we investigated how variations of the stimulus properties across time are reflected in brain activity. In study 1, the stimulus was repeated twice and we accordingly observed two successive negative deflection over frontal region in response to stimulus presentation. **In study 2, we played simultaneously two speech streams that differ by the variations of their sound envelope across time**. We could thus compare how much the brain activity reflected the processing of each auditory streams and investigate how attention could amplify the cortical encoding of sensory information. In study 3, we found the emergence within the brain activity of a 10 Hz rhythm corresponding to the target frequency for all conditions during wakefulness.

An alternative approach to study sensory processing during sleep is to look into how stimuli impact ongoing sleep processes (Blume et al., 2017; Züst et al., 2019). In study 1, we show that the brain oscillation evoked by our stimulus was present even after stimulus offset due to resonance properties of the brain at a slow-wave frequency during NREM sleep (Steriade, 2000). **We uncovered in study 2 that selective processing differed in the first and second part of the stimulation during REM sleep while the amount of eye movements remained constant, suggesting the presence of other mechanisms involved in the gating of selective processing during REM sleep**.

A last possibility for decoding sensory processing during sleep is to rely on the interpretation of markers of cognitive processes. **In study 1, we provide further evidence that establish evoked slow-wave activity as a reliable marker of semantic associations across NREM sleep** (Canales-Johnson et al., 2020; Züst et al., 2019). In study 2, we show that eye movements are a reliable marker of reduced responsiveness during REM sleep. We furthermore uncover a parallel in sensory gating between eye movement and slow waves. These results show a dissociation between sensory gating and variations of consciousness levels. Indeed, slow waves have been proposed to be responsible for the reduction of consciousness during NREM sleep, while the presence of eye movement is rather characterized by more vivid imagery and thus enhanced conscious activity. An intriguing question is whether the similarity between slow and rapid eye movements extends to sensory integration and whether sensory integration also dissociates from variations of consciousness levels, as it was found for sensory gating.

6.2.3 BCI as creating a new connection with the sleeper

An open question in our paradigms is the generalizability of our results and how much they depend on the particular experimental settings and stimulation procedure. Across our studies, we relied on a task induction approach, where subjects automatized a task before entering to sleep. **Task induction could be crucial in setting the right cognitive mindset to process external stimuli during sleep**. The fact that our mindset before sleep affects sleep vigilance is examplified by the the first night effect, during which sleeping in a new environment leads to increased sensitivity to its external stimuli (Agnew et al., 1966). The presence of a brain mode allowing to remain vigilant during sleep has been differently characterized as the stand-by mode, the sentinel or the night-watch mode (Tamaki et al., 2016; Blume et al., 2018; Legendre et al., 2019; Tamaki & Sasaki, 2019). While sleep might have been shaped by evolution, vigilance during sleep could also be shaped by cognitive processes and reveal the ability of the brain to flexibly adapt to external demands even once asleep.

The BCI here developed allows to further detect slow waves and couple sensory stimulations to ongoing neural activity. Doing so, BCI can bypass voluntary control of the subject and allow for the direct investigation of mechanisms controlling vigilance during sleep. **If internal brain processes supporting vigilance can be decoded and predicted, stimuli can be finely tuned to ongoing brain processes to control for their encoding, or conversely their suppression**. Thus, closed loop procedure allows for the creation of new interactions with the sleeping brain that can be explored for both scientific and practical purposes.

The development of ambulatory EEG devices coupled with automated analyses and stimulus presentation could be an interesting way to test for the generalizability of our results in other conditions than the laboratory settings. The study 3 was totally automized and could, in principle, be performed outside the laboratory. Such procedure could drastically enhance the amount empirical data collected, allowing for a more comprehensive understanding of vigilance across several nights and ecological contexts. **Closed-loop stimulation and ambulatory EEG are thus a promising avenue for sleep research**.

6.3 Outlook

6.3.1 Consciousness science

My PhD thesis is a typical example of how transdisciplinary approaches allow to overcome the limitations of respective disciplines in cognitive science. **Here, we relied on neuroimaging to uncover the realization of psychological processes during sleep in the absence of behavioural reports**. In parallel to my sleep research, I also used insights from psychology to solve two problems of philosophy of mind. In interaction with Institut Jean Nicod at the ENS (Paris), I tackled the paradox of fiction using a psychological framework of emotion regulation (Koroma, 2018). During three months at Monash University (Melbourne) of my thesis, I relied on the predictive theory of mind to address the meta-problem of consciousness, a philosophical debate investigating the origin of the hard problem of consciousness (Koroma, 2019). Drawing on the value of methodological and theoretical cross-talks among disciplines of cognitive science, I was involved in ALIUS, an international research group studying the diversity of consciousness.

Consciousness is difficult to tackle as a scientific object and within ALIUS, we consider that consciousness science would benefit from an interdisciplinary approach to understand its multi-faceted nature (Figure 46). This research group connects with an interested audience inside and outside academia during ALIUS workshops and the annual Bulletin that features interviews with prominent researchers investigating the diversity of conscious states (Hohwy & Koroma, 2017; Fox & Koroma, 2018; Bayne et al., 2019). Burning issues in consciousness research are discussed at these occasions and the exchange of ideas is facilitated within the scientific community. **This further allows for an emerging community of researchers to establish the study of the diverse aspects of consciousness, sleep included, as an outstanding research topic**.

Yet, no unifying theorical approach consensually explains to this day how psychological and neural processes support the diversity of consciousness. **I applied to postdoctoral funds in order to study sleep and consciousness based on a complex systems approach in GIGA-consciousness (Liège).** I will use existing open-source datasets of neural recordings during sleep to characterize sleep states based on metrics derived from the study of complex systems. Considering sleep as a dynamical process, I will tackle the diversity of sleep sequences. Finally, using unsupervised approaches, I will investigate whether novel states that might be overlooked by traditional scoring methods can be uncovered by studying the dynamics of sleep patterns.

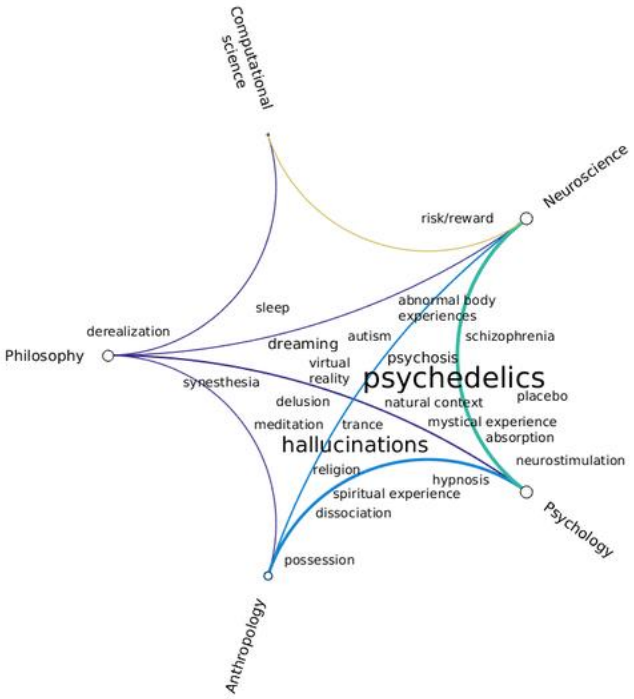


Figure 46 **Map charting the research interests of ALIUS members**. Lines between each discipline show the multidisciplinary nature of the research conducted by ALIUS members. Research items were located according to the disciplinary fields of the researchers studying these topics. Word size is scaled according to the number of ALIUS members studying each item.

6.3.2 Open science

My research is guided by the incentive of the research production system to get novel and striking results and publish in high-impact journals. For example, what determined the choice of Japanese stimuli in my first project is not only guided by scientific consideration. Indeed, by using pseudo words, we could have ensured that people were never exposed to semantic associations to be learnt. Yet, using Japanese translations was rather intended to strike the imagination and fulfill a scientific fantasy. **We got scooped but our study provides new evidence for sleep learning with an original methodology**. Relying on both pragmatic adaptation to the publishing system and scientific interests is a strategy that I learned throughout this thesis and hope valuable for the pursuit of my career.

The publishing format also had specific constraints. Scientific publications inherit from the printed format and are called papers. It is constructed as a story that should be fully explained. Yet, part of the results of study 2 concerning the intra-trial dynamics of reconstruction rendered the story

more complex and did not fit the word limitations for a report. Thus, they were not included in the publication. These results will potentially never be published (except as part of this manuscript). **A certain amount of experimental data is not systematically reported in the current publishing system, leading to a limited representation of the research results.**

The Open science movement analyzed the needs of scientists within the publishing system in order to develop other ways of sharing research outputs that are complementary to the editorial process (Foster & Deardorff, 2017). **One example is preprints that can be deposited on open access archives**. Upon submitting our article to Current Biology, editors offered a "sneak peak" option, that allows readers to access the papers that are currently under review behind a paywall. Major publishing system adapts to the evolution of the scientific production, yet they do not fully endorse the principles of open science that fostered the development of these tools.

6.3.3 Ecological science

In a context of rarefaction of resources, the need to reduce, reuse, recycle and recover data are met by the open science framework. Collaborative experiments and preregistration allow to reduce the amount of data acquired by collectively deciding and designing experiments. Accessibility of data and source codes allows for their reuse by fostering the reproducibility of results. It allows also to ask novel research questions based on existing datasets. Finally, adopting standardized methods allows to make datasets compatible and makes meta-analysis easier (see Figure 47 for an illustrative metaphor of an open-science scientific production). **Open-science favors collaborative and robust research practices adapted to current ecological challenges.**

By focusing on collaboration, open science is also a vector of scientific innovation. Using a model of cooperation, Muthukrishna and Henrich (2017) argued that scientific innovation is actually largely fueled by the collective and cooperative culture rather than individual achievements (Muthukrishna & Henrich, 2016). For example, the Flynn effect, the fact that IQ score raised over the last century, was proposed to be due to increased interconnectedness and openness in our culture rather than other biological factors (Nisbett et al., 2012; Muthukrishna & Henrich, 2016). Most importantly, cognitive diversity and accurate transmission of knowledge and ideas are key factors of innovation. These are values that I intend to promote in my future research.

While promoting innovation, recent reforms of the French research system overtly valued

competition between researchers and planned on concentrating funds on fewer researchers. **Taking part to the opposition to these reforms, I founded the "Laboratoire de la Grrr…Eve", where I applied my knowledge on sleep to conduct real-life experiments designed to probe the collective consciousness of ENS and foster political awareness of the situation** (Nap attack, APPENDIX).

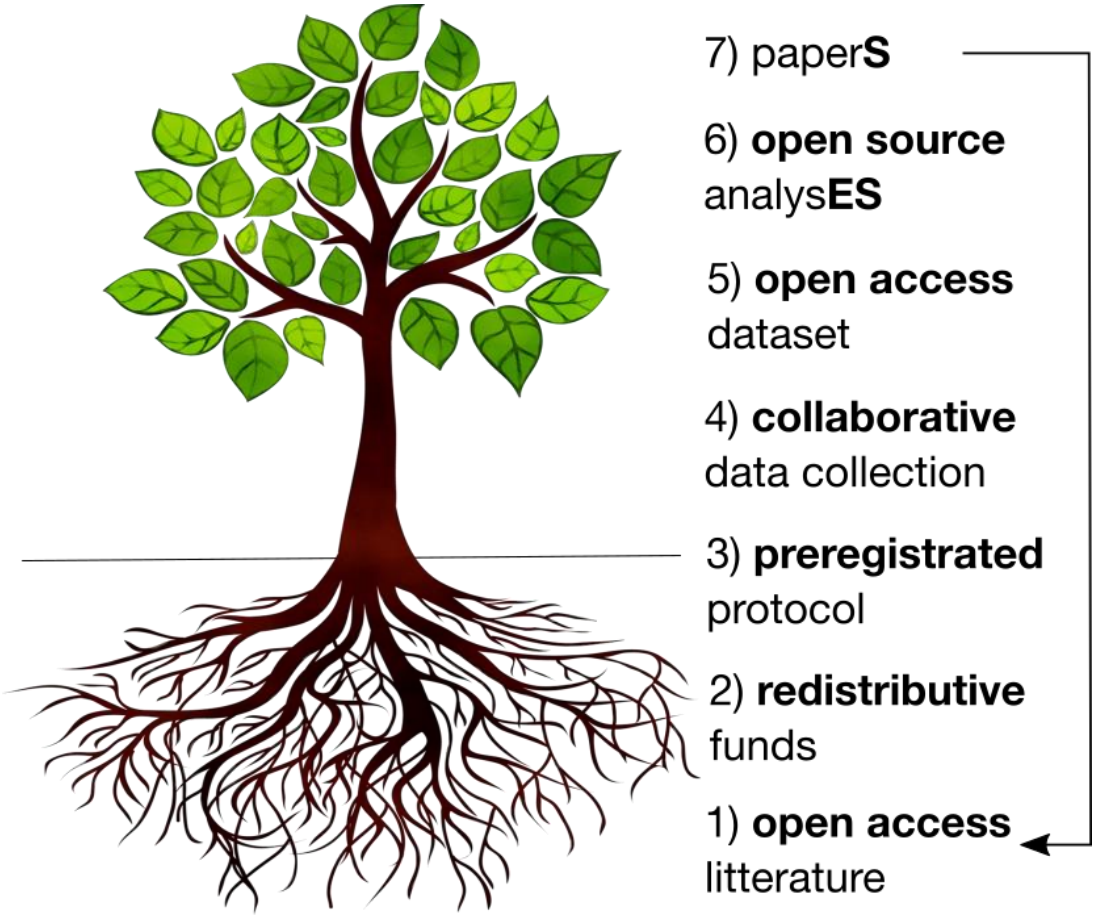


Figure 47 **The tree of knowledge: a metaphor for an open-science scientific production.** The roots represent the scientific knowledge and resources that can be used to develop a new scientific question. These are discussed among pairs to design collaboratively the experiments for which an adequate level of resource can be gathered. The trunk represents the scientific paradigm that can be investigated across multiple labs. The branches represent different analytical strategies that can lead to different papers based on the same dataset. Because analysis codes would be accessible, contributions to the analysis of the dataset can be initiated from anywhere in the analytical process. Similarly, anybody can contribute to data gathering in adding new subjects to the experiment thanks to standardized experimental methods and adequate meta-data to track the different factors at play (e.g., age of participants). This model is scalable as the same process can be applied for meta-analyses gathering data across several paradigms.

7 APPENDIX

« NapAttack »

Preliminary study (14h-16h in the corridors of ENS):

Scientific question: What is the semantic network of the collective consciousness at ENS?

Protocol: People met in the corridor of the ENS were invited to take part of the study and answered to 3 questions:

1) "Which word does evoke the current situation to you?"
2) "Where to put it on the map?"
3) "To which other word should it be related?"

Results: This data collection (n=48) resulted in a map with 48 spatially distributed and interconnected items (Figure 48)

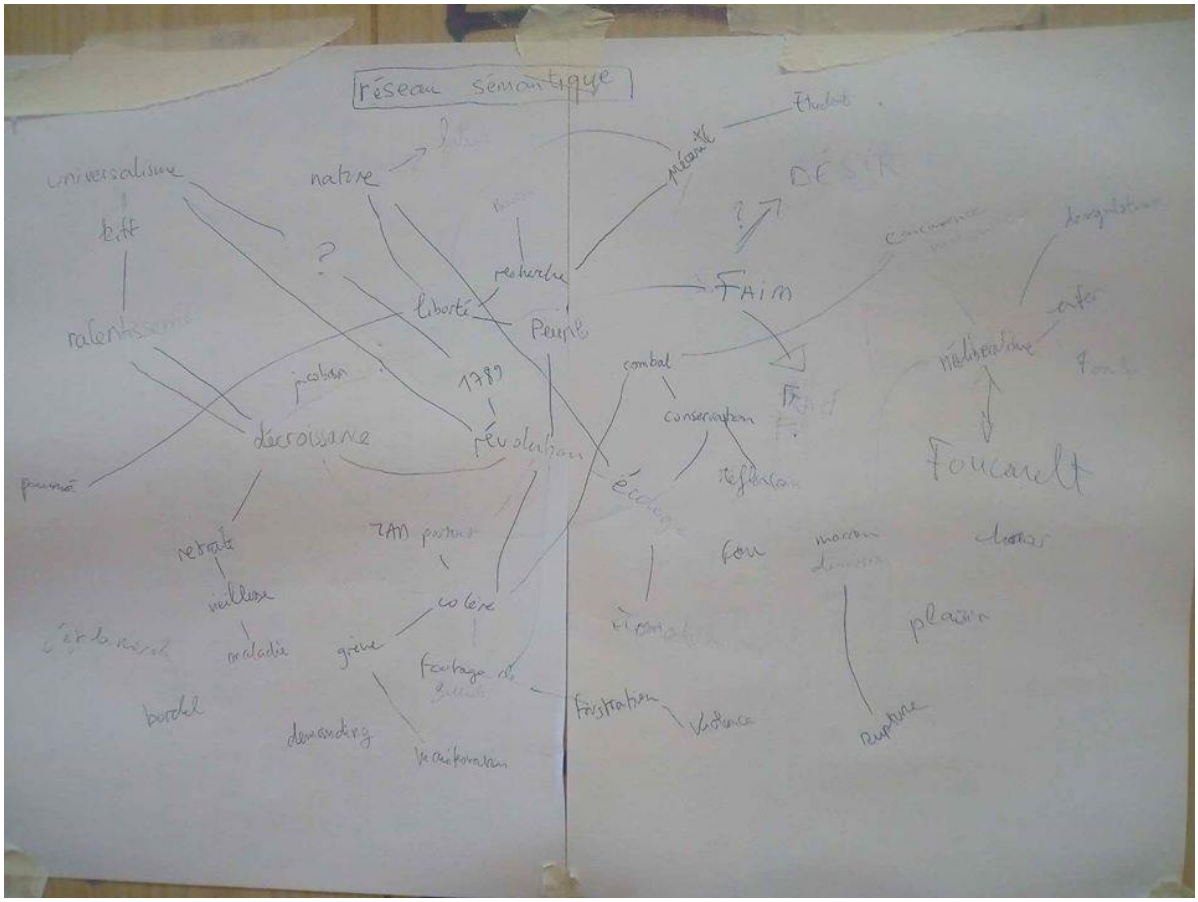


Figure 48 **Raw semantic map collected in the corridors of the ENS**. Straight lines represent the connections between items.

Study (14h-16h in the corridors of ENS):

Scientific question: Which meaningful relationships can be extracted from the semantic network of the current situation collected at ENS?

Protocol: To do so, we simulated sleep replays and renormalization processes inspired from the sleep litterature (Wilson & McNaughton, 1994; Tononi & Cirelli, 2003). The semantic map obtained from the Preliminary Study was encoded as a conjunction matrix in Matlab (Mathworks, Inc.). The values linking two items were defined as follows:

$P_{xy}=(1/d_{xy} + 2*r_{xy})/(\Sigma_{xy}(d_{xy} + 2*r_{xy}))$

P_{xy}, value in the conjunction matrix defining the strength of the link between item x and item y, and defined as 0 for the same item to avoid that an item can reactivate itself

d_{xy}, Euclidian distance on the semantic map between item x and item y

r_{xy}, presence of a link between item x and item y on the semantic map. r=1 if present, r=0 if not.

$\Sigma_{xy}(d_{xy} + 2*r_{xy})$, normalization procedure to obtain a probability map summing to one.

This resulted in a map of probability of transition from any item x to any item y. We thus computed "replays" consisting in a sequence of reactivation of items from this map. The initial reactivated item for each replay was chosen randomly. Then, the probability for picking the next word is determined as its probability of transition plus a random factor. When the item x is reactivated, the probability of the next reactivated item (y) is defined as follows: $P_y=P_{xy}+2*R*max(P_{xi})$, R being a random factor uniformly distributed between 0 and 1, $max(P_{xi})$ being the highest probability of transition between x and all other items to scale it across all items. The item with the highest score is selected. After fifty reactivated items, i.e. one replay, the sequence is terminated and a connection is reinforced between the three items that have been reactivated the most during the replay. The conjunction matrix is then renormalized so that all of its values sum to 1. A new replay is then initiated randomly. After ten minutes of replays, i.e. one nap, the process is stopped. To start a new nap, the conjunction matrix was reinitialized to its initial form. Six naps were run in total. The connection between items of the conjunction matrix are plotted using the circular graph function (Kassenbaum, 2020). Pictures illustrating the reactivated items were taken from online databases.

Results: The whole procedure was projected in real time on the walls of the corridor of ENS (Figure 49). The three items that have been reactivated the most for each nap constituted a triplet of words (Figure 50). Six triplets, i.e. one for each nap, were formed at the end of the experiment.

Figure 49 **Result of one replay**. During the projection, words appeared sequentially on the map on the top panel. The size of the word corresponds to the number of times one item has been reactivated. At the end of the replay, the three most reactivated items and their images appeared (bottom panel). A new connection between these items is added before initiating the next replay.

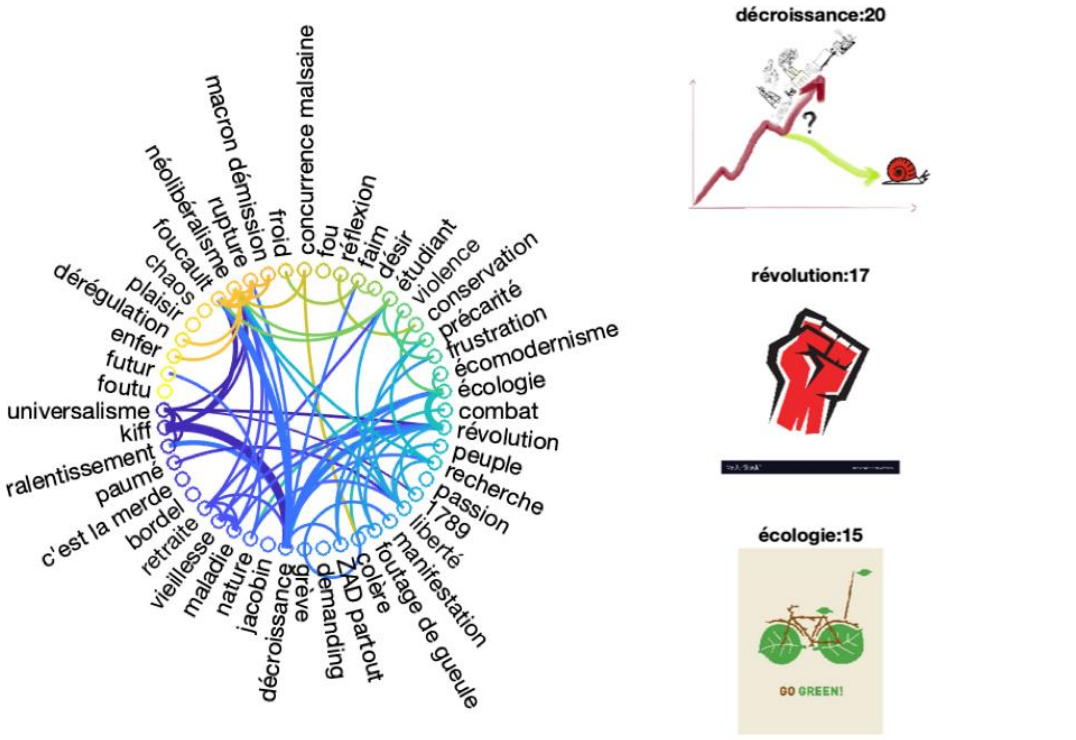


Figure 50 **Result of one nap**. On the left panel, connections between the different items at the end of one nap. Color and size encode the strength of the connections. On the right panel, the three items that have been reactivated the most during the nap, forming a triplet, are represented.

Results: The results of the six naps were:

- macron demission, strike, rupture
- freedom, nature, disease
- kiff, degrowth, nature
- strike, rage, neoliberalism
- universalism, revolution, kiff
- degrowth, revolution, ecology

Discussion: To investigate how meaningful were the triplets for the people at ENS, we relied on the election at the majority judgment. This voting procedure is empirically informed and avoids classical paradoxes of collective decision (Balinski & Laraki, 2011). 15 anonymous participants contributed to the vote on an online platform (Figure 51).

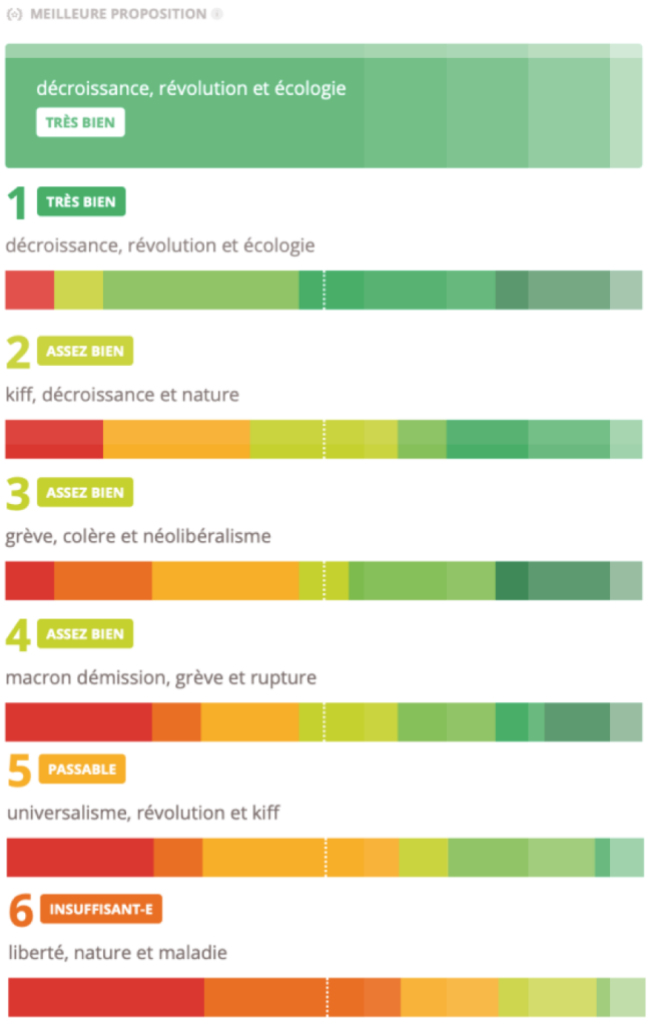


Figure 51 **Results from the Majority Judgment**. Participants selected for each choice between seven options: excellent, very good, good, rather good, average, insufficient, to reject (n=15)

Conclusion: The favored triplet at ENS is "degrowth, revolution and ecology"

Materials availability:

All codes are available: https://cloud.disroot.org/s/Gggsp2G6bJTsmfL

All stimuli are available: https://cloud.disroot.org/s/4yFPopBwYjYtJy3

All results are available: https://cloud.disroot.org/s/STEsQ6HD6xy96g7

Vote on the online platform can be consulted here: https://tinyurl.com/yc6s34fp

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AUTHOR CONTRIBUTIONS

STUDY 1 - sleep learning of semantic associations

The author was involved in the study design, data acquisition, data analysis and writing the manuscript. Sid Kouider was involved in the study design, analysis, and writing the manuscript. Damien Léger was involved in the analysis and providing experimental settings. Maxime Elbaz was involved in providing experimental settings.

STUDY 2 – selective suppression of informative speech during rapid eye movements

The author was involved in the study design, data acquisition, data analysis and writing the submitted manuscript. Sid Kouider, Célia Lacaux, Thomas Andrillon and Guillaume Legendre were involved in the study design, analysis, and writing the manuscript. Maxime Elbaz was in involved in providing experimental settings.

STUDY 3 - information integration across slow waves

The author was involved in the study design, data acquisition, data analysis and writing the manuscript. Sid Kouider, Jean-Maurice Leonetti and Irene Echeverria Altuna were involved in the design of the protocol, analysis, and writing the manuscript. Damien Léger was involved in the analysis and providing experimental settings. Maxime Elbaz was in involved in providing experimental settings.

APPENDIX

The author was involved in the study design, data acquisition, data analysis and writing the manuscript.

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RÉSUMÉ

Le sommeil est un mystère pour l'esprit conscient. En effet, quand on dort, soit la conscience s'en trouve diminuée et peu de souvenirs en reste le jour suivant. Soit la conscience est modifiée au cours des rêves et son souvenir nous frappe par son incongruité. Que se passe-t-il donc quand on dort ? Dans cette thèse, nous avons présenté des sons complexes pour étudier comment le cerveau interprète les informations du monde extérieur pendant le sommeil. On s'est posé la question de comment la déconnection du dormeur par rapport à son environnement sensoriel dépend des processus cognitifs en cours survenant dans le sommeil. Pour cela, on a utilisé l'EEG, une technique d'enregistrement de l'activité cérébrale. On a pu ainsi montrer que non seulement le cerveau continue d'écouter les sons pendant le sommeil, mais aussi qu'il peut sélectivement amplifier ou supprimer certaines informations et même apprendre une langue étrangère. Ces capacités dépendent néanmoins de façon cruciale de certains marqueurs cérébraux de l'activité interne du dormeur, démontrant que le sommeil est un processus fondamentalement actif et le siège d'une activité cognitive complexe.

MOTS CLÉS

EEG, Attention, Sommeil, Vigilance, Perception, Mémoire

ABSTRACT

Sleep is a mystery for the conscious mind. Indeed, whilst being asleep, either consciousness is reduced and few memories remain upon awakening. Or consciousness is altered during dreams and memories struck us by their incongruity. What happens then when we sleep? In this thesis, we played complex sounds to study how the brain interprets information from the external world during sleep. We asked ourselves how the sleep disconnection from its sensory environment depends on cognitive processes occurring during sleep. To do so, we used EEG, a brain imaging technique. We could show that the sleeping brain keeps on monitoring sounds and can even selectively enhance or suppress certain information, as well as learn a foreign language. These capacities depend nevertheless crucially on markers of internal activity during sleep, demonstrating that sleep is a fundamentally active process and host of complex cognitive

KEYWORDS

EEG, Attention, Sleep, Vigilance, Perception, Memory