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Using magneto-encephalography to assess the processing depth of auditory stimuli in the sleeping human brain

Mélanie Strauss

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Université Paris Descartes

Ecole Doctorale Frontières du Vivant

THESE

Soutenue publiquement le 26 novembre 2015 pour obtenir le grade de

DOCTEUR EN SCIENCES

Spécialité: NEUROSCIENCES

**ETUDE MAGNÉTO-ENCÉPHALOGRAPHIQUE DE LA
PROFONDEUR DU TRAITEMENT DE L'INFORMATION
AUDITIVE PENDANT LE SOMMEIL**

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THESIS

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DOCTOR IN PHILOSOPHY

Specialty: NEUROSCIENCES

**USING MAGNETO-ENCEPHALOGRAPHY TO ASSESS THE
PROCESSING DEPTH OF AUDITORY STIMULI IN THE
SLEEPING HUMAN BRAIN**

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ABSTRACT

Sleep can be defined as a behavioral state of rest in which consciousness of external stimuli vanishes and responsiveness to the environment is drastically reduced. When we sleep, however, we may still react and wake up to our name or to the alarm clock, suggesting that some processing of external stimuli remains. We address in the present work the question of how deeply external information is processed during sleep.

We recorded brain activity in adult human subjects simultaneously in electro and magnetoencephalography (EEG and MEG) in response to auditory stimulation, before, during and after a short period of sleep. In order to test information integration through the brain hierarchy, we focused on hierarchical predictive coding capabilities, which enable the brain to anticipate the future from previous knowledge. Predictions occur at many if not all steps of the cortical hierarchy. Testing different levels of predictions enables us to assess the steps at which information integration is disrupted during sleep.

We first tested the capacity of the sleeping brain to detect auditory novelty. We analyzed brain responses to violations of local and global temporal regularities, which are respectively reflected in EEG during wakefulness by two successive prediction error signals, the mismatch negativity (MMN) and the P300. Our analysis revealed that both the MMN and the P300 vanish during sleep, along with the loss of activations in prefrontal and parietal associative areas. The MMN gradually decreased in the descent to sleep, whereas the P300 vanished abruptly with the loss of awareness during N1 sleep. This all-or-none behavior strongly reinforces the hypothesis that the P300 is a marker of consciousness. Even so, we showed that sounds still activate sensory cortices, and that the brain remains able to detect new sounds and to habituate to them, but only in the limited context of sensory adaptation.

Having demonstrated the disruption of predictive coding for arbitrary and newly acquired statistical regularities, in a second set of experiments we tested the capacity of the sleeping brain to develop predictions of future auditory stimuli for over-learned semantic knowledge stored in long-term memory. We presented sleeping subjects with simple arithmetic facts such as “two plus two is nine” and recorded brain responses to correct or incorrect results. We discovered that the sleeping brain was still able to detect arithmetic violations, with activations in part similar to wakefulness. We suggest that, although sleep disrupts explicit arithmetic computations, there is a preservation of prediction error signals for arithmetic facts stored in long-term memory.

The present work clarifies the steps at which auditory information integration is disrupted during sleep, and which cognitive functions remain or vanish. The preservation of low-level sensory

adaptation and of predictions from long term memory may account for the residual responsiveness that can be observed during sleep, while subjects are unconscious. Finally, these results also help to better understand why a given stimulus may or may not be processed during sleep. The depth of information integration is function of the ongoing spontaneous oscillations of the sleeping brain, but also of the nature of the stimulus, i.e. its salience, its knowledge, and its relevance.

RÉSUMÉ

Le sommeil est défini comme un état comportemental de repos où nous perdons conscience de notre environnement et notre réactivité aux stimuli extérieurs est drastiquement réduite. Pourtant, lorsque nous dormons, l'appel par notre prénom ou à la sonnerie du réveil peuvent encore nous réveiller, suggérant qu'un certain degré de traitement des stimuli reste possible. Dans ce travail, nous soulevons la question de la profondeur du traitement de l'information extérieure pendant le sommeil.

Nous avons enregistré simultanément l'activité cérébrale de sujets sains adultes en électro- et magnéto-encéphalographie (EEG et MEG) en réponse à des stimulations auditives, avant, pendant, et après une courte période de sommeil. Afin de tester la profondeur du traitement de l'information à travers la hiérarchie corticale, nous nous sommes concentrés sur les capacités de codage prédictif hiérarchique, qui permettent au cerveau d'anticiper les événements futurs à partir d'une connaissance passée. Les prédictions sont faites à de nombreuses étapes de la hiérarchie corticale. Tester les différents niveaux de prédiction nous permet donc d'évaluer précisément à quel niveau l'intégration de l'information est interrompue.

Nous avons d'abord testé les capacités du cerveau à détecter la nouveauté auditive. Nous avons présenté aux sujets des séquences de sons comprenant des régularités temporelles à courte (locale) ou à longue (globale) échelle de temps, et analysé les réponses cérébrales à des sons violant ces régularités. Les réponses cérébrales à ces violations locales ou globales se traduisent respectivement en EEG à l'éveil par l'émergence de deux signaux d'erreur de prédiction : la négativité de mismatch (MMN) et la P300. Notre analyse révèle que la MMN et la P300 disparaissent toutes deux dans le sommeil avec la perte des activations des aires associatives préfrontales et pariétales. Au cours de l'endormissement, la MMN diminue progressivement, tandis que la P300 disparaît brutalement avec la perte de conscience des stimuli. Ce comportement tout-ou-rien renforce l'hypothèse que la P300 est un marqueur de la conscience. Malgré tout, nous avons montré que le cerveau détecte toujours les nouveaux sons et peut s'y habituer, mais seulement dans un contexte limité d'adaptation sensorielle de bas niveau.

Après avoir démontré la perte des capacités de codage prédictif dans le sommeil dans le cadre de régularités statistiques arbitraires et nouvellement acquises, dans une deuxième série d'expériences nous avons testé la capacité du cerveau endormi à établir des prédictions sur les sons à venir dans le cadre de connaissances sémantiques connues déjà stockées en mémoire à long terme. Nous avons présenté à des sujets endormis des opérations arithmétiques simples, comme "deux plus deux égal neuf", et nous avons enregistré les réponses cérébrales aux résultats corrects et aux résultats faux. Nous avons découvert que le cerveau était toujours capable de détecter les violations arithmétiques

dans le sommeil, avec des activations en partie similaires à celles de l'éveil. Nous suggérons que, bien que le sommeil prévienne tout calcul explicite, il y a conservation des signaux d'erreur de prédiction pour les opérations arithmétiques simple déjà mémorisées.

Ce travail clarifie à quel niveau l'intégration de l'information auditive est interrompue pendant le sommeil, et quelles fonctions cognitives persistent ou s'altèrent. La persistance de l'adaptation sensorielle et des capacités de prédiction à partir de connaissances déjà mémorisées sont probablement responsables de la réactivité résiduelle qui peut être observée pendant le sommeil alors que les sujets sont inconscients. Finalement, ces résultats aident aussi à mieux comprendre pourquoi un stimulus donné sera traité ou non dans le sommeil. La profondeur de l'intégration de l'information est fonction des activités spontanées du cerveau dans le sommeil, mais aussi de la nature du stimulus, à savoir sa saillance, sa connaissance, et sa pertinence.

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Abbreviations:

NREM sleep: non-rapid eye movement sleep

NREM1: non-rapid eye movement sleep stage 1

NREM2: non-rapid eye movement sleep stage 2

NREM3: non-rapid eye movement sleep stage 3

REM sleep: rapid eye movement sleep

REMs: rapid eye movements

SWS: slow wave sleep

SWA: slow wave activity

EEG: electroencephalography

MEG: magnetoencephalography

fMRI: functional magnetic resonance imaging

PET: positron emission tomography

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I. INTRODUCTION

Sleep is a recurrent state of rest which has been robustly conserved throughout evolution in all the animal kingdom. Everyone experiences sleep and its typical transient loss of awareness of the external world. Amazingly, we also instantaneously recover this awareness when we wake up, with sometimes the feeling of coming back from a very deep black out, or sometimes from an intense and rich oneiric world. Brain activity does not stop during sleep. Cerebral rhythms change to enable the brain to operate multiple metabolic and cognitive functions that may require to be disconnected from the environment. Among others, the sleeping brain replays and reprocesses memories that have been previously learnt during wakefulness in order to consolidate them in long term memories and generate more accurate internal models of the world. However, the brain cannot be completely disengaged from outside, as we need to wake up in case of dangerous or any other relevant situations. The alarm clock of daily life is an obvious and recurrent example. Thus, in addition to internally generated stimuli, the brain also processes some information from the environment during sleep. However, very little is known about the nature and the depth of this processing.

The question of how deeply information is processed during sleep has a specific interest in sleep research, but also in the study of consciousness in general. The scientific study of consciousness has been a growing field over the last 20 years. One of its major issues has been to determine what is specific to consciousness and what can be done unconsciously. It appears that conscious access to information strongly influences how deeply this information will be processed. Nevertheless, there is growing evidence to support the idea of an efficient non-conscious processing in several cognitive domains. Cognitive functions have been tested in a variety of non-conscious conditions, such as subliminal masking, anesthesia, in disorders of consciousness (DOC) as vegetative state patients, and for few of them in sleep. For methodological reasons, most of studies have been performed in healthy subjects in subliminal conditions, as they do not receive medication, do not require clinical monitoring and, crucially, can answer whether they are conscious or not of presented stimuli. Sleep can bring several advantages as a model for the study of non-conscious processing. Firstly, it is a recurrent physiological state experienced every day by everybody, unlike anesthesia or DOC patients. Secondly, its rapid induction and reversibility enables testing and retesting of subjects over multiple sessions. Thirdly, sleep is sustained in time and enables the use of longer lasting stimuli, for several seconds and more, unlike most of subliminal paradigms. However, if sleep appears as a non-conscious state regarding the environment, the presence of dream mentation reveals a striking dissociation between the consciousness of the external world, and an inner form of consciousness. This aspect should then be taken into account for the study of information processing during sleep.

The absence of overt behavior has long been a barrier to the study of sleep and its related cognitive processes. However, recent advances in brain imaging now enable us to assess which kind of information is processed during sleep, and how deeply this information is processed. We had to wait for the development of electroencephalography (EEG) at the beginning of the 20th century and, a few decades later, for the first electrophysiological description of sleep in 1935 (Loomis et al. 1935). Today, we benefit from a large range of functional neuroimaging methods, with increasingly precise spatial and temporal resolution, which have finally opened a window on the sleeping brain.

During my PhD, I have therefore chosen to take advantage of these new methods to address the question of how deeply information is processed during sleep. As an introduction to my work, I will first briefly define sleep with its general physiology and functions, and present the main ideas about consciousness, its neural signatures, and which cognitive processes can be performed non-consciously. Then, I will detail the literature on spontaneous brain activities during sleep to better understand the physiological activations of the sleeping brain through sleep stages and their consequences on consciousness and information integration. We will see that sleep may not be a 'pure' non-conscious model. I will then review the existing knowledge on sensory and cognitive processing of external information during sleep. Finally, I will present my chosen methodology to further improve our understanding of the depth of information processing during sleep, in terms of imaging methods and cognitive paradigms, and why they can bring new advantages compared to previous studies.

I.1. SLEEP – A RECURRENT NON-RESPONSIVE STATE

I.1.1. What is sleep?

Sleep is a recurrent physiological state of rest occurring every night. From a behavioral standpoint, sleep is defined by four criteria: *i*) a reduced motor activity, *ii*) a reduced sensory responsiveness to external stimuli, *iii*) a stereotyped posture (in humans, lying down with eyes closed) and *iv*) a relatively rapid reversibility. The reduced sensory responsiveness distinguishes sleep from quiet wakefulness, and other criteria from anesthesia, coma or hibernation.

Sleep occurrences are governed by circadian and homeostatic regulations (Borbély 1982). Circadian rhythms regulate the periodicity of the wakefulness-sleep cycle within the 24 hours and are mainly synchronized by light (LeGates et al. 2014). Homeostatic regulation results in increased sleep pressure with the time spent awake (Dijk et al. 1990). Sleep deprivation and increased sleep pressure lead to sleepiness and a subsequent deeper sleep that corresponds to the sleep ‘rebound’.

Sleep is associated with modifications of cerebral rhythms and activations that were progressively described over the 20th century. EEG modifications during sleep were first reported by Loomis et al. in 1935, with the description of spindles and slow rhythms characteristic of light and deep sleep. In 1953, Aserinsky and Kleitman reported rapid eye movement (REMs) activities during sleep along with the re-activation of EEG rhythms (Aserinsky and Kleitman 1953; Aserinsky and Kleitman 1955). With Kleitman, Dement then described the systematic and cyclic occurrence of ‘REM sleep’ after light and deep sleep and its association to dreams (Dement and Kleitman 1957). The description of this new stage of sleep was completed by Jouvet who reported the associated muscular atonia (Jouvet and Michel 1959), found its origin in the pontine brain stem (Jouvet 1962) and started to describe it in neurochemical mechanisms (Jouvet 1969; Jouvet 1972).

In 1968, Rechtschaffen and Kales published a classification of sleep stages based on 30-seconds epochs of electrophysiological recordings of cerebral, ocular and muscular activities (Rechtschaffen and Kales 1968). It used to be the worldwide reference until the publication of few new modifications in 2007 by the American association of Sleep Medicine (American Academy of Sleep Medicine and Iber 2007). Sleep is now defined by four different stages which occur successively within a cycle: Non-Rapid Eye Movement sleep stage 1 (NREM1), NREM stage 2 (NREM2), NREM stage 3 (NREM3) also named Slow Wave Sleep (SWS) and Rapid Eye Movement (REM) sleep. Commonly the term light sleep refers to NREM2 and deep sleep to NREM3/SWS. Sleep cycles are repeated along the night following an ultradian (<24h) rhythms, about every 90 minutes. The first part of the night is richer in SWS sleep and the second in REM sleep.

I.1.2. Definition of sleep stages

Sleep stages differ by their EEG, electro-muscular (EMG) and electro-ocular (EOG) activities. I will review later in more detail their specific EEG rhythms, but here are the main general features for each of them.

NREM1 refers to the initiation of sleep, i.e. the process of falling sleep. The EEG alpha rhythms (8 – 12 Hz) characteristic of eyes-closed and quite wakefulness progressively disappear (alpha suppression) to leave theta rhythms (4 – 8 Hz). Ocular fixation is lost, leading to slow eyes movements recorded in the EOG. The muscle tone can be still high.

NREM2 is defined by the occurrence, on a background of theta rhythms, of specific sleep figures, the K-complexes and sleep spindles. K-complexes are the highest physiological brain potentials in amplitude, exceeding 100 μ V. They are better recorded in anterior areas. Spindle are waxing and waning oscillations between 12 and 18 Hz that do not last more than 2 seconds. In this stage the brain metabolism decreases, breathing and heart rates become slow and regular. Some muscle tone may persist.

Along with the depth of sleep, delta activity (< 4 Hz) and slow oscillations (slow waves < 1Hz) increase progressively. NREM3/SWS is reached when slow waves are recorded in more than 20% of the 30-seconds epoch used for sleep scoring. This slow delta activity is predominant in frontal areas. Note that SWS can't be differentiated from anesthesia and pathological slow waves in coma. Brain metabolism is very low, breathing and heart rates are slow and regular.

REM sleep is characterized by a sudden increase in EEG rhythms within theta and alpha ranges, very similar to NREM1 activities, but associated with rapid eye movements and a complete loss of muscular tone. Only some twitches of the extremities are recorded. Breathing and heart rate are increased and more variable, and males frequently develop erection. Brain metabolism is closed to the one in wakefulness.

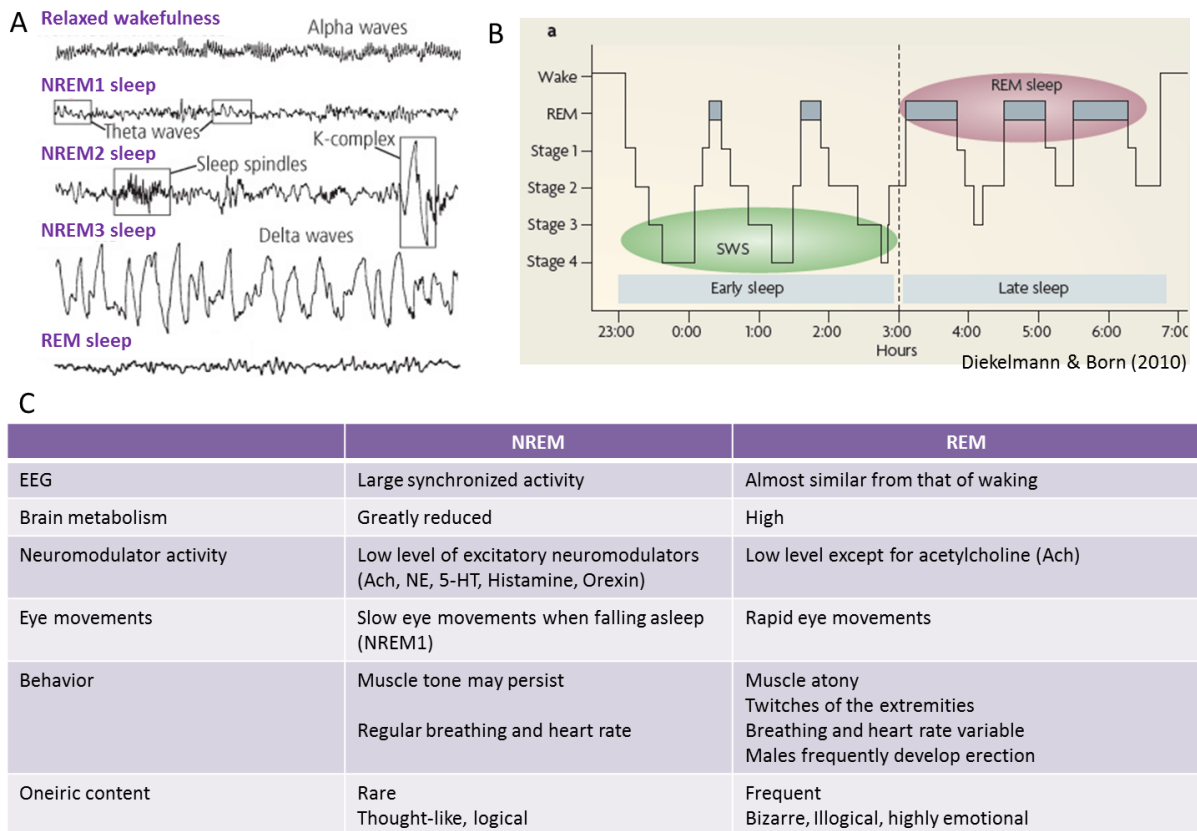


Figure 1. Sleep stages.

A. EEG modifications across sleep stages.

B. Evolution of sleep cycles during the night. The early part of the night is richer in NREM3 or Slow Wave Sleep (SWS), the late part in REM sleep.

C. Physiological modifications in NREM and REM sleep.

I.1.3. Overview of sleep functions

Mammals, birds, fishes, and even fruit flies sleep (Siegel 2008), and humans spend up to one third of their life asleep. We may therefore speculate that sleep plays a crucial role in the regulation of organisms. After sleep deprivation, we lack of attention, our cognitive performances decrease, we become irritable and sensitive (Killgore 2010; McCoy and Strecker 2011; Arnal et al. 2015). In addition, we are more susceptible to infections (Bryant et al. 2004; Faraut et al. 2012a), and after chronic sleep deprivation, at higher risk of metabolic and cardio-vascular disease (Copinschi 2005; Faraut et al. 2012b; Bayon et al. 2014; Leger et al. 2015). Why we sleep is still an open question, but growing evidence demonstrates numerous functions in metabolism, energy conservation, immune system regulation, development, synaptic plasticity, memory and cognitive functions. Our goal here is not to provide an extensive review of all these functions, which may be found elsewhere (Siegel 2005; Cirelli and Tononi 2008), but to summarize some main ones. Indeed, better understanding of the role of sleep may also help to understand another striking question: why do we lose consciousness during sleep?

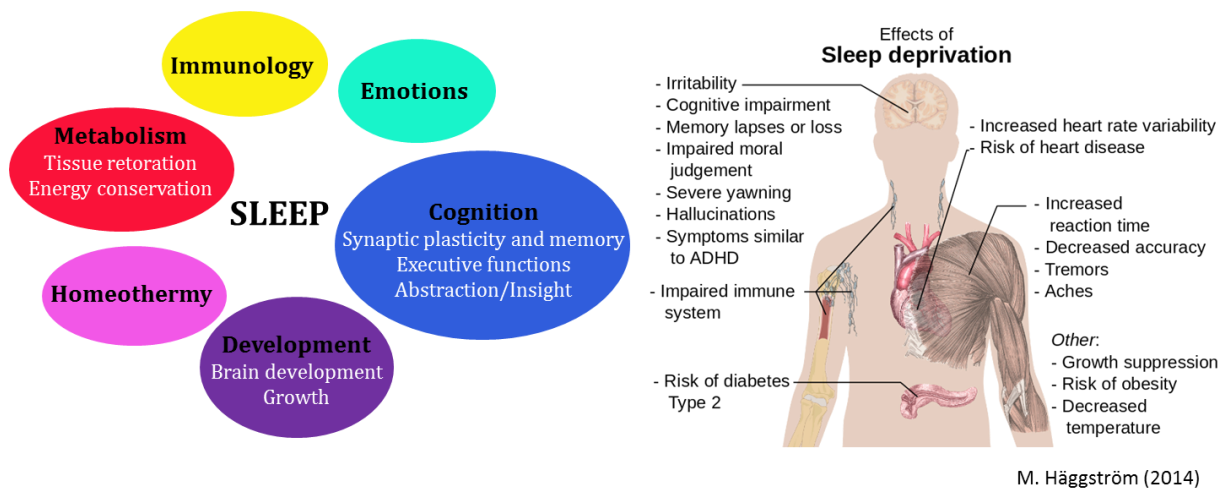


Figure 2. Sleep functions and effects of sleep deprivation

Metabolism

Sleep is primarily believed to play an important role in metabolism and energy regulation, as it obviously represents a state of rest with less energy expenditure than during wakefulness. After intense activity during waking (especially for the brain, which spends more than 20% of the whole body's energy), sleep is believed to be necessary for performing cellular maintenance and preventing long term damage (Vyazovskiy and Harris 2013). Earlier studies showed that rats which are subject to total sleep deprivation die from caloric and thermal dysregulation (Rechtschaffen et al. 1989), strengthening the homeothermic role of sleep. Sleep is also believed to maintain integrity of the neuro-immune endocrine system (Bryant et al. 2004; Faraut et al. 2012a; Gómez-González et al. 2012).

Brain development

During infancy and childhood, the development of sleep patterns follows the development of brain maturation. For example, the development of slow wave activity (SWA) through brain areas is similar to the development of synaptic density (Shaw et al. 2008; Kurth et al. 2010). Both present a peak before adolescence and evolve following a postero-anterior axis. Thus, the maturation of specific skills in children can be predicted by the topographical distribution of slow waves activity (Kurth et al. 2012). REM sleep also is modulated throughout the development. It is overrepresented at birth and its proportion on total sleep time decreases progressively through ages. REM sleep is believed to promote synaptic formation, necessary to brain growth and maturation (Marks et al. 1995; Bridi et al. 2015).

Synaptic homeostasis

Even after childhood, sleep continues to play a role in synaptic homeostasis throughout life. A balance must be achieved between continuing to acquire new information and creating new synapses on the one hand, and the costs of increased synaptic strength on the other hand, such as the need for energy, for metabolic supplies, increased cellular stress, decreased selectivity of neural responses and saturation of the ability to learn (Tononi and Cirelli 2014; Vyazovskiy and Faraguna 2015). Sleep is then believed to play a crucial role in synaptic homeostasis, in decreasing the synaptic density after its previous increase during wakefulness. This has been formulated by Tononi and Cirelli in their synaptic homeostasis hypothesis (SHY) (Tononi and Cirelli 2003; Tononi and Cirelli 2006; Tononi and Cirelli 2014). They propose that synaptic homeostasis is the fundamental role for sleep, or in their words: “sleep is the price we pay for plasticity”.

Memory consolidation

Abundant evidence indicates that memories are better consolidated after a night of sleep (or even a nap) than after the same period of wakefulness. Several comprehensive reviews can be found on this topic (Maquet 2001; Peigneux et al. 2001a; Stickgold 2005; Diekelmann and Born 2010; Rasch and Born 2013). I will merely summarize the main hypotheses and results here. All different types of memories: declarative, procedural or emotional, benefit from sleep. It has been shown that NREM sleep is strongly involved in declarative and explicit hippocampal-dependent memories (for example Gais and Born 2004). Indeed, during NREM sleep, we know from animal studies that information learned during wakefulness is replayed at the cellular level in the hippocampus (Pavlides and Winson 1989; Wilson and McNaughton 1994). In humans at the scalp level, this replay is thought to be reflected in slow waves and spindle activity, which both correlate with memory performances after sleep (Huber et al. 2004; Gais et al. 2002; Schabus et al. 2004). REM sleep has been suggested to play an important role in non-declarative types of memory, such as procedural (Plihal and Born 1997; Maquet et al. 2000; Walker et al. 2002), perceptual (Karni et al. 1994) and emotional aspects (Wagner et al. 2001; Nishida et al. 2009; Baran et al. 2012) of memory. Yet, the respective roles of NREM and REM sleep are probably not so independent. The succession of both sleep stages could be necessary for the effective consolidation in long term memories, as suggested by the sequential hypotheses (Scrima 1982; Giuditta et al. 1995; Ambrosini and Giuditta 2001; Diekelmann and Born 2010; Rasch and Born 2013). For example, the ‘active system consolidation’ hypothesis (Diekelmann and Born 2010; Rasch and Born 2013) suggests that newly acquired memory traces, which are repeatedly re-activated during SWS during the hippocampal replay, would become progressively redistributed within the neocortex to ‘prime the relevant networks’ for synaptic consolidation during subsequent REM sleep. Indeed, emerging evidence reveals that REM sleep plays a crucial role in the creation and strengthening of cortical synaptic connections (Blanco et al. 2015). Sleep would then not serve uniquely to downscale synaptic density (synaptic homeostasis hypothesis, Tononi and Cirelli 2003;

Tononi and Cirelli 2006; Tononi and Cirelli 2014), but would also enable to select, strengthen or create new synapses in order to consolidate adequate memories into existing knowledge. We will come back on physiological correlates of memory consolidation later in this manuscript.

Information restructuring, insight and creativity

In addition to memory consolidation, the sequence NREM-REM sleep would also lead to the formation of new and more effective associations, leading to abstract generalization and extraction of rules and invariants from new learnt materials (Walker and Stickgold 2010; Diekelmann and Born 2010; Lewis and Durrant 2011). Experimental evidence is indeed growing for the role of sleep in enhancing problem solving and the ability to find hidden rules, and in transferring implicit learning into explicit knowledge (Wagner et al. 2004; Durrant et al. 2013; Nieuwenhuis et al. 2013; Wilhelm et al. 2013; Beijamini et al. 2014; Sterpenich et al. 2014; Friedrich et al. 2015). For example, Wagner et al. (2004) asked subjects to perform a number reduction task in which they were presented with a sequence of numbers and had to apply a succession of simple rules to find a final number. They were not instructed about a hidden rule enabling to rapidly find the final number before the end of the sequence. Subjects either subsequently slept 8h, or stayed awake for the same period of time (during the night or during the day). Subjects who slept gained insight into the hidden rule more than twice as much as those who stayed awake, then suggesting that sleep promotes rule extraction and the formation of explicit knowledge.

Moreover, new created associations would lead to foster creativity (Cai et al. 2009; Ritter et al. 2012), a role which is believed to be largely subtended by REM sleep and dreams. Cai et al. (2009) presented subjects with a Remote Associates Test (RAT): three words were presented to the subject, who had to find a fourth one associated with the three words (“e.g., cookies, sixteen, heart: ; the answer is sweet: cookies are sweet, sweet sixteen, sweetheart”). The ability to find the fourth word was improved after a nap with REM sleep, compared with quiet rest and non-REM sleep, suggesting that REM sleep enhances the formation of associative networks.

Virtual reality and predictive generator

Dreaming may also influence waking behavior. Jouvett has defended for a long time the hypothesis that REM sleep and dreams would be “the guardian of psychological individuation” (Jouvett 1992). Instinctual behaviors, genetically programmed, would be rehearsed every night in order to maintain thorough life individual psychological stability. Another theory was proposed by Revonsuo, the ‘Threat Simulation Theory’, where dreams, as in a virtual reality program, would serve to simulate threatening events in order rehearse threat perception and threat avoidance (Revonsuo 2000). Finally, Hobson and Friston (Hobson et al. 2014) developed this virtual reality hypothesis, also considering dreaming as a generator of fictive experiences of rich and vivid environments, which would help to anticipate challenging situations and to adapt waking behavior. More precisely, they

interpreted this notion in term of free energy minimization: dreaming would serve as a predictive generator that, freed from sensory bottom-up inputs, would simulate what could happen in wakefulness in order to minimize prediction errors in the brain, optimize internal models of the world and eventually minimize complexity. The idea that a ‘sleep phase’ disconnected from sensory bottom-up inputs, i.e. characterized by the loss of consciousness of the environment, is necessary for reprocessing information, learning and generating more accurate predictions about the waking environment is not new, and was formulated in the framework of unsupervised neural networks earlier (Hinton et al. 1995).

To summarize, loss of external awareness during sleep would then be necessary for consolidation and restructuring of newly acquired memories, enabling the generation of more accurate internal models of the world to eventually minimize complexity and energy.

I.2. CONSCIOUS AND NON-CONSCIOUS PROCESSING

Starting from its behavioral definition, sleep is a non-responsive state that is typically classified as non-conscious. However, the existence of dream mentation reveals a notable dissociation between the reduced responsiveness and the apparent loss of consciousness of the surroundings on the one hand, and the preservation of some forms of internal awareness on the other hand. Also, from a physiological standpoint, sleep is not homogeneous but composed of various brain rhythms and activations that are modulated across time and brain regions to serve specific functions; activations that can reach, for some of them, the level of wakefulness (Braun et al. 1997). The *a priori* non-conscious state of sleep has then to be better evaluated. Inasmuch as the precise nature of consciousness during sleep has a potential strong impact on external information processing.

Consciousness is however quite difficult to assess precisely during sleep. The absence of overt behavior prevents to assess the mental content of sleeping subjects, and reports upon waking are function of the integrity of memory formation and retrieval. To try to better characterize the state of consciousness during sleep, we then need to proceed with an indirect approach. First, we need to know which neural bases are associated with consciousness from the study of other conscious and non-conscious states in the laboratory, and then, assess whether those signatures of consciousness are preserved or disrupted during sleep.

In this section, I will review the first step of this approach. I will summarize the current hypotheses on the neural signatures of consciousness, and then briefly review the cognitive functions that may be performed with and without consciousness.

I.2.1. Conscious state versus conscious content

Consciousness is a complex and equivocal notion. Classically in the scientific community, consciousness is approached by distinguishing the *state* of consciousness from the *content* of consciousness (Laureys 2005). The state of consciousness refers to the level of arousal or vigilance. The content of consciousness refers to the subject's perceptions, to what he is aware of and what he can report.

Laureys et al. (2005) proposed a schematic representation of those two components, using the term *arousal* for the level or state of consciousness, and *awareness* for the content of consciousness (see figure X.). In most of the clinical situations, arousal and awareness evolve together. They are both present during wakefulness but absent in deep sleep, coma or anesthesia. In some cases, however, arousal and awareness are dissociated, as in vegetative state, where subjects are awake but not aware;

or inversely, in REM sleep where subjects are not awake but may report conscious content from their dreams.

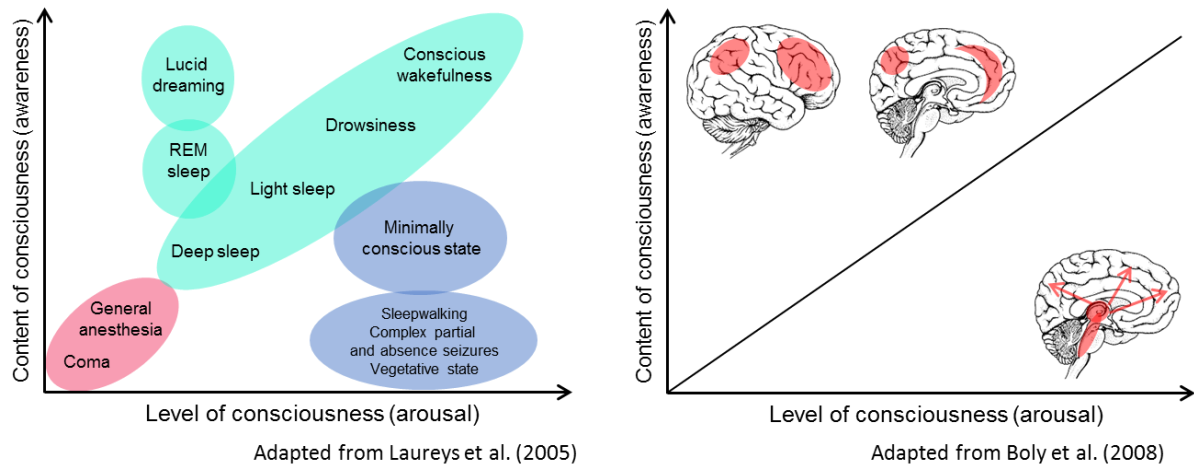


Figure 3. Level and content of consciousness.

Left. During normal sleep, the level and the content of consciousness evolve together, except in REM sleep, in which the content of consciousness is increased compared to the low arousal (Laureys 2005).

Right. The level of consciousness is believed to be subtended by the ascending arousal system (brain stem – thalamus), and the content of consciousness by cortico-cortical interactions, especially the fronto-parietal network (Boly et al. 2008; Dehaene and Changeux 2011)

However, even the term *arousal* is ambiguous (Picchioni et al. 2013). First, it may refer to *physiological activations* of the brain, starting from the ascending reticular activating system (ARAS) (Laureys et al. 2009) to associated activations of thalamo-cortical, autonomic and endocrine systems. Indeed, the physiological modulation of this ascending activating system leads to switches in vigilance states as in sleep and its lesion to coma. Second, it may refer to the *behavioral responsiveness* to stimuli, as when behavioral responses are used to measure arousal in coma scales, or arousal threshold during sleep (Rechtschaffen et al. 1966). Let's not forget that sleep, by definition, is a loss of responsiveness. This confusion between physiological activations and responsiveness makes the notion of arousal very vague and somewhat tricky to use, as there is actually no direct correlation between physiological activations and responsiveness. For example, what about arousal in REM sleep, when no behavioral responses are emitted, while the thalamo-cortical activity is very high? We will then try in this manuscript to explicitly refer when needed to either brain activations or behavioral responsiveness. When used, the term arousal will refer to physiological activations in the ascending

activating system (brain stem – thalamus – cortex). Also, we will use the term *vigilance* when referring to wakefulness and the different stages of sleep (states of vigilance).

Considering the content of consciousness (we will use the term *awareness*), the notion is not less ambiguous and debated. Admittedly, it refers to the first-person subjective experience, the perceptions that we are aware of. However, some authors consider as conscious only the perceptions that can explicitly be *reported* (Dehaene et al. 2006), whereas some others consider as conscious all *phenomenal* experiences that the subject may intuitively perceive, being able to report them or not (Block 2005; Lamme 2006). The first view has the advantage to easily assess conscious representations experimentally. In any case, cortico-cortical interactions are believed to play a crucial role in awareness, as we will see below. Finally among awareness, *external awareness* has been differentiated from *internal awareness*, depending on whether the perceived experience refers to external stimuli or to internal, environmental stimuli-independent thoughts (Vanhaudenhuyse et al. 2010). Vanhaudenhuyse and collaborators suggested that external awareness is associated with activations of lateral fronto-parietal cortices, while internal awareness would lead to more medial activations in the precuneus, posterior cingulate, anterior cingulate, mesiofrontal cortices, and parahippocampal areas.

1.2.2. Neural signatures of consciousness

Recent advances in neuroimaging methods have enabled neuro-anatomic and functional approaches of consciousness. In contrasting activations of conscious versus non-conscious stimuli, either in manipulating the content of consciousness or in the different states of consciousness, experimental approaches led to the emergence of hypotheses on neural signatures or correlates specific to conscious access. Several models have been proposed (Seth 2007), which I will only summarize here by briefly listing the main neural signatures that have been highlighted by the majority of models.

Distributed network

Except for rare localizationist models of consciousness (Lau 2007; Zeki 2007; Ward 2011), most theories refer to consciousness as a unitary phenomenon emerging within a *distributed* cortical network of long-range connectivity, where the information is made available to a large number of sensory and associative areas. A largely accepted view is indeed that the brain is organized in multiples independent specialized modules that can process information non-consciously and in parallel (Fodor 1983; Baars 1988; Shallice 1988). Baars (1988) first introduced the notion that information would access consciousness if it was ‘globally distributed’ or broadcasted through a significant numbers of modules within a ‘global workspace’, enabling the modules to interact with each other and share information. Later, several models have proposed brain interpretations to this

workspace, conferring to different structures the critical role of interconnecting the specialized modules. Some conferred to the thalamo-cortical system the central role for information integration and consciousness (Llinás et al. 1998; Tononi and Edelman 1998; Edelman and Tononi 2000; Tononi 2004; Tononi and Koch 2008). Others did recognize the thalamus as an important relay for information integration, but conferred the critical role to the cortex, and especially to the long-distance prefronto-parietal network (Dehaene et al. 1998a; Dehaene and Naccache 2001; Dehaene et al. 2006; Dehaene and Changeux 2011).

Several experimental results indeed revealed fronto-parietal activations specific to conscious conditions. For example, large fronto-parietal activations were elicited following conscious stimuli but not after subliminal ones in masking paradigms (Beck et al. 2001; Dehaene et al. 2001; Sadaghiani et al. 2009). Fronto-parietal deactivations were also described in various non-conscious states, as in anesthesia (Kaisti et al. 2002), in epilepsy (Blumenfeld et al. 2004; Blumenfeld 2005; Blumenfeld et al. 2009), or in disorders of consciousness patients (Laureys et al. 2009; Vanhaudenhuyse et al. 2010).

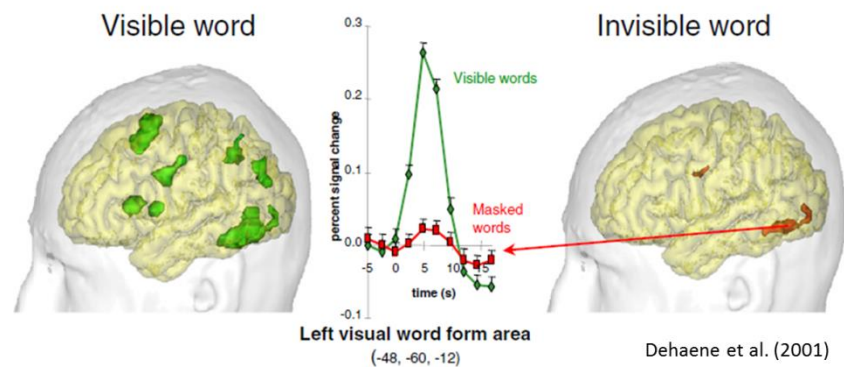


Figure 4. Brain activations following a conscious and a non-conscious stimulus.

Left. Conscious words elicit largely distributed activations, with fronto-parietal activations and amplification of sensory-related areas, here the left visual word form area.

Right. Unconscious words elicit small activations in sensory-related areas, without recruiting higher-level associative regions.

Information sharing and synchrony

Information sharing has often been associated with consciousness, as it may enable to ‘bind’ together the multiple features of sensory information into a unique percept (Tononi 2004; Lamme 2010; Dehaene and Changeux 2011). Synchronization of activities within the same frequency range has been proposed as an efficient physical way to integrate and share information across distinct groups of neurons. Neural synchrony through fast oscillations, in the beta and gamma ranges, has frequently been considered as a feature of consciousness in several models (Llinas and Ribary 1993;

Engel and Singer 2001; Varela et al. 2001; Tononi and Koch 2008; Ward 2011; Dehaene and Changeux 2011).

Still in minimally contrasting conscious and non-conscious stimuli, experimental results indeed revealed a significant increase in beta and gamma range frequencies after conscious stimuli (Tallon-Baudry et al. 1997; Summerfield et al. 2002; Wyart and Tallon-Baudry 2008; Gaillard et al. 2009). Also, the loss of consciousness in anesthesia and coma is associated with a marked decrease in high frequencies along with the emergence of large slow oscillations (Chander et al. 2014; Chennu et al. 2014).

Recurrent top-down processes

Beyond synchrony, recurrent activity supported by top-down connections is thought to play a crucial role in consciousness in most models of consciousness (Llinás and Paré 1991; Lamme and Roelfsema 2000; Edelman and Tononi 2000; Crick and Koch 2003; Tononi and Koch 2008; Dehaene and Changeux 2011). Recurrent activations from higher-order areas would mainly serve to share and maintain information through long distant perceptual areas.

For example, Lamme and collaborators distinguish two steps in information integration (Lamme and Roelfsema 2000): a first ‘feedforward sweep’ of non-conscious activations from sensory cortices to associative areas (potentially up to the prefrontal cortex), followed by secondary recurrent processes within activated cortical areas that would enable to share the different features of information (e.g. orientation, color ... of a visual percept) across regions and bind those features into a unified coherent percept. The feedforward activations would occur non-consciously, while recurrent activation would be equivalent to consciousness.

For Tononi and collaborators, recurrent activations within the thalamo-cortical system (‘dynamic core’) would enable high differentiation (‘the availability of a very large number of conscious experiences’) and integration (‘the unity of each such experience’) of information, both considered as fundamental properties of conscious information (Tononi 2004). The more the information is integrated, the more the information is conscious, as measured by a continuous mathematical value ‘phi’ (Φ).

In the Global Neuronal Workspace model developed by Dehaene and collaborators, recurrent top-down processes are necessary for the amplification and the maintenance of sensory information within the workspace critical for conscious access (Dehaene et al. 1998a; Dehaene and Naccache 2001; Dehaene et al. 2006; Dehaene and Changeux 2011). Thus, to summarize this last model of consciousness with previously described signatures, authors proposed that conscious access depends on i) the sudden all-or-none ‘ignition’ of a large cortico-cortical network including the prefronto-parietal cortices, named the ‘global neuronal workspace’ (GNW), ii) the maintenance and sharing of the information across the GNW through recurrent top-down loops and synchronization at

beta and gamma frequencies, which then lead to iii) late and sustained amplification of sensory activations. Importantly, the ignition of the GNW and amplification of sensory information would depend on top-down *attention* on sensory information. They then suggest that sensory processes that potentially carry enough activation for conscious access but lack top-down attentional amplification may stay at a preconscious level.

Empirically, conscious access in masking paradigms correlates with activations in high-order associative areas, which are also associated with amplifications of sensory activations (Dehaene et al. 2001; Haynes et al. 2005; Del Cul et al. 2007). In disorder of consciousness patients, impaired top-down connections have been suggested as the main explanation for the loss of consciousness (Boly et al. 2011a; but see King et al. 2011 and Boly et al. 2011b for methodological discussion). The crucial role of attention has been demonstrated by attentional blink (Shapiro et al. 1997) and inattention blindness (Mack 2003) paradigms, which manipulate attention to prevent consciousness of visible stimuli.

Late and sustained activations

Probably as a consequence of top-down processes – which occur after bottom-up sensory integration –, and revealing information maintenance, consciousness is believed to be associated with late and sustained activations arising a few hundred milliseconds after stimulus presentation (Dehaene et al. 1998a; Dehaene et al. 2006; Lamme 2006; Lamme 2010; Dehaene and Changeux 2011).

A neural signature which is believed to index this late and sustained conscious activation is the P300 (Sutton et al. 1965), a posterior positive potential elicited around 300 ms after the presentation of perceived stimuli (Hillyard et al. 1971; Squires et al. 1975b). Hillyard and collaborators compared evoked potentials to the same physical stimulus when it was consciously perceived or not. They could demonstrate that only conscious stimuli elicited the P300. At the contrary, early components as the N1 were preserved in both conscious and non-conscious conditions. Later, the P300 was divided in two different positivities, the P3a and the P3b. The P3a is earlier and transient (around 240 ms), located in anterior regions in scalp EEG, whereas the P3b (around 350 ms) is sustained in centro-posterior areas (Squires et al. 1975b). Actually, the P3b (the proper P300) appears to best index consciously perceived stimuli (Squires et al. 1973; Squires et al. 1975a; Squires et al. 1976; Vogel et al. 1998; Sergent et al. 2005; Del Cul et al. 2007; Polich 2007). Some reserve can yet be issued when considering the P300/P3b as a signature of consciousness. Firstly, later activations may also index the maintenance of perceptual information for reporting purpose, and not purely conscious access (Pitts et al. 2012; Pitts et al. 2014). Secondly, the P300 has also been found in a few studies in subliminal conditions (Bernat et al. 2001; Brázdil et al. 2001; Lamy et al. 2009), although strongly decreased in amplitude and much more localized in space.

Metacognition and metaconsciousness

Finally, consciousness may be consciousness of a perception, but also consciousness to be conscious. Some authors stressed this distinction between first-order consciousness and higher-order or meta-consciousness, giving to reflective thoughts and judgments a crucial role (Hobson and Pace-Schott 2002; Lau 2007; Cleeremans et al. 2007; Hobson 2010). For example, in one of the few models that integrates sleep into its theory of consciousness, Hobson and collaborators (Hobson and Pace-Schott 2002; Hobson 2010) distinguished a primary or proto-consciousness from a secondary-form of consciousness. The primary consciousness would correspond to perceptions and emotions, but without volition, self-reflection, insight, judgment or abstract thoughts that would characterize the secondary consciousness. The primary consciousness could be the one experienced in dreams, when brain activation is high. However, the secondary consciousness would emerge only if activities in cortical structures are modulated appropriately, as when aminergic projections are activated during wakefulness. This model highlights the importance of neurochemical modulation. Others have pointed out the role of anterior and dorso-lateral parts of prefrontal cortices in metacognition and metaconsciousness (Fleming and Dolan 2012).

1.2.3. The extent of non-conscious processes

As proposed by some models (Llinás et al. 1998; Tononi and Edelman 1998; Edelman and Tononi 2000; Tononi 2004; Tononi and Koch 2008; Dehaene et al. 1998a; Dehaene et al. 2006; Dehaene and Changeux 2011), conscious access of presented information is associated with its global broadcasting and integration among large networks in the brain through sustained recurrent activations. Conscious information can thus be maintained in working memory, be shared within multiple cognitive domains, be manipulated – especially through prefrontal recruitment – into executive systems to be evaluated, to generate novel combinations of operations and eventually be encoded in long term memory. Consciousness is also associated with the spontaneous generation of intentional behavior. In contrast, processing of unconscious information is thought to be transient, labile and localized within modular sensory processors. This dichotomy predicts large differences between cognitive processing of conscious and unconscious stimuli. However, growing evidence suggests that even if it remains largely modular, unconscious processing occurs within a large range of cognitive domains.

1.2.3.1. Sensory, motor, and cognitive domains

Subliminal paradigms revealed that unconscious stimuli are processed at the sensory level, as demonstrated largely for visual (Dehaene et al. 2001; Fang and He 2005; Jiang et al. 2007), but also

auditory (Sadaghiani et al. 2009; Diekhof et al. 2009; Kouider et al. 2010) or tactile (Blankenburg et al. 2003; Taskin et al. 2008) modalities, eliciting significant fMRI activations in related sensory cortices. Even under deep anesthesia, sounds largely activate auditory areas (Plourde et al. 2006; Davis et al. 2007; Liu et al. 2012).

Beyond sensory cortices, emotional subliminal stimuli can elicit amygdala activity (Morris et al. 1999; Pasley et al. 2004; Dannlowski et al. 2007) or modulate its activity after subsequent conscious stimuli (Whalen et al. 1998; Nomura et al. 2004). Those emotional unconscious stimuli are behaviorally relevant as they can lead to fear conditioning (Morris et al. 1999) and decrease conscious access threshold compared to neutral ones (Gaillard et al. 2006).

In other domains, number magnitude estimation and related parietal activations (intra parietal sulcus) have been demonstrated for masked numbers (Naccache and Dehaene 2001).

Subliminal words can be processed at the orthographic, lexical and even semantic level (Dehaene et al. 2001; Dehaene et al. 2004a; Devlin et al. 2004; Nakamura et al. 2005; Gaillard et al. 2006; Van den Bussche et al. 2009; Kouider et al. 2010; Qiao et al. 2010), eliciting activation in the left fusiform gyrus (Dehaene et al. 2001; Nakamura et al. 2005; Gaillard et al. 2006) and especially in the visual word form area (Qiao et al. 2010). In EEG, unconscious semantic integration has also been assessed by means of the N400, a centro-posterior negative potential elicited after semantic violations (Kutas and Hillyard 1980). The N400 has been shown to be modulated or elicited by unconscious stimuli in attentional blink (Luck et al. 1996; Vogel et al. 1998) or masking experiments (Kiefer 2002; Kiefer and Brendel 2006; van Gaal et al. 2014), and has also been recently recorded in vegetative and minimally conscious patients (Rohaut et al. 2015). Interestingly, word-pair associations could also be encoded in memory and retrieved unconsciously (Reber et al. 2012).

Moreover, unconscious stimuli may enter the motor domain, as they modulate (Leuthold and Kopp 1998) and even elicit (Dehaene et al. 1998b) EEG signatures of motor preparation, the lateralized-readiness-potentials, in pre-central areas.

Cognitive functions usually associated with executive systems and consciousness may also occur automatically. Unconscious inhibition (Gaal et al. 2010), conflict adaptation (van Gaal et al. 2010b) and cognitive control (Lau and Passingham 2007) may be performed with associated activations in the inferior and even dorsolateral prefrontal cortex. The anterior cingulate cortex has also been shown to be activated in unconscious error detection (Hester et al. 2005; Ursu et al. 2009). Furthermore, Pessiglione and collaborators showed that motivation can be elicited non-consciously (Pessiglione et al. 2007), subliminal cues of monetary value bias decision making (Pessiglione et al. 2008) and judgments as estimation of value and confidence can be automatically performed (Lebreton et al. 2015).

1.2.3.2. Novelty detection

Finally, auditory novelty may be detected unconsciously. When a new deviant sound is presented in a series of standard ones (the so-called ‘oddball paradigm’), it elicits two successive neural events in EEG: the mismatch negativity (MMN), a fronto-central negative component peaking at around 100–250 ms after stimulus deviance (Näätänen et al. 1978), followed by the P300 previously described.

We previously saw that the P300 has been found in a few studies using subliminal conditions (Bernat et al. 2001; Brázdil et al. 2001; Lamy et al. 2009), challenging the classical view of the P300 as a signature of consciousness. At the exception of those studies, this late positive potential is classically absent in non-conscious conditions (for example Comerchero and Polich 1999; Sergent and Dehaene 2004; Bekinschtein et al. 2009).

The MMN, at the contrary, is much more frequently found in non-conscious conditions. Although of strongly reduced amplitude, the MMN has been recorded after subthreshold or unattended stimuli (Allen et al. 2000; Diekhof et al. 2009; Näätänen 1990), during anesthesia (Koelsch et al. 2006) and in disorders of consciousness (Bekinschtein et al. 2009; King et al. 2011). It is then commonly believed to reflect pre-attentive automatic processes (Näätänen et al. 2001).

However, we should here moderate or precise this view of the MMN as an automatic component, when considering the very mixed results on the presence of the MMN in unconscious conditions. During anesthesia, most of studies failed to detect the MMN (Plourde 1991; Simpson et al. 2002; Heinke et al. 2004), and one among them even showed the abolition of the MMN before the subjective loss of consciousness (Simpson et al. 2002). In disorders of consciousness patients, results considerably vary and the MMN is only found in average in about 10 to 25% of vegetative state (VS) patients (for meta-analyses see Fischer et al. 2004; Daltrozzi et al. 2007). For example, Fisher et al. (2010) found a MMN in only 5/27 permanent VS patients, Bekinschtein et al. (2009) in 1 out of 4 VS, and Faugeras and al. (2012) did not find a significant MMN in VS but a strongly diminished one in minimally conscious patients. Finally, it appears that the MMN can occur unconsciously, but is not an automatic or systematic component of unconscious states. Actually, it seems to more accurately reflect a prognosis marker of recovery: it is more frequently found in MCS than in VS patients, and its amplitude increase with the level of consciousness from VS to MCS patients, and in correlation with further recovery (Fischer et al. 2004; Naccache et al. 2005; Daltrozzi et al. 2007; Wijnen et al. 2007; Qin et al. 2008; Faugeras et al. 2011).

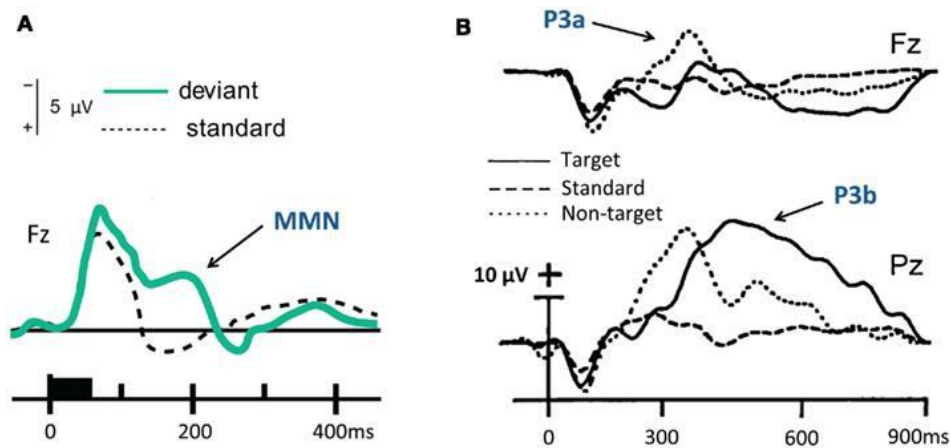


Figure 5. MMN, P3a and P3b/P300

A. MMN is evoked by deviant tones (1032 Hz, 20%) versus standard tones (1000 Hz); from (Sams et al. 1985)

B. P3a and P3b/P300 following non-target (500 Hz) and target (2000 Hz, 10%) tones in a series of standard ones (1940 Hz); from (Comerchero and Polich 1999)

If the MMN can be found in non-conscious conditions, the precise cognitive mechanisms which subtend the MMN are still debated. Indeed, effects following deviant tones may be explained by two different functional mechanisms: sensory adaptation and predictive coding. When series of identical sounds are repeated, brain responses to the sound progressively decrease, a repetition-suppression mechanism known as habituation or sensory adaptation (Desimone 1996). The presentation of a new sound will then lead to activate new ‘fresh afferents’ and will elicit a stronger (as the original) brain response. This sensory adaptation effect is then passive, emerging from bottom-up activations. However, the effect observed after deviant tones may also emerge from active top-down mechanisms: the brain may have learnt the rule embedded in the standard sequence tone (‘sound A is always followed by A’) and have then *predicted* the following tone (sound A). The unexpected rare tone (sound B) will then lead to a prediction error signal, at the origin of a deviance effect recorded in EEG (Friston 2005). Those two mechanisms, sensory adaptation and prediction, are then confounded in the oddball paradigm, and the crucial difference between passive bottom-up or active top-down processes cannot be easily distinguished. This led some authors to consider the MMN as the reflect of sensory adaptation (Ulanovsky et al. 2003; May and Tiitinen 2010), and others as the reflect of prediction (Garrido et al. 2009; Farley et al. 2010; Todorovic and de Lange 2012; Wacongne et al. 2011; Wacongne et al. 2012; Lecaiguard et al. 2015). We will see later that our experiment enables to precisely resolve this issue, showing that the proper MMN reflect the prediction error signal, while earlier and later effect of the mismatch response reflect adaptation (Strauss et al. 2015).

SUMMARY OF KEYS POINTS

Consciousness has two main dimensions:

- The *state* or level of consciousness refers to the state of *vigilance*, i.e. wakefulness, sleep, or coma. Behaviorally, it can be assessed by the level of responsiveness to the environment (coma scale, awakening threshold during sleep). Its modulation is subtended by the level of arousal or activation in the ascending activating system (brain stem – thalamus – cortex axis). Importantly however, no direct correlation between physiological activations and responsiveness has been established.

- The *content* of consciousness, or awareness, refers to what the subject is conscious of. It is assessed by asking the subject the content of his perceptions. We also distinguish external from internal awareness, depending on whether the perceptions refer to stimuli of the environment or to inner perceptions or thoughts. They are believed to be subtended by cortico-cortical interactions.

Both state and content of consciousness have been used to determine specific brain signatures associated with consciousness. They are characterized by *late* and *sustained recurrent* activations, largely *distributed* through long-distant brain networks and oscillating in the *beta and gamma frequency range*. Those activations enable to share information across multiple brain areas to form a unique conscious percept that can be maintained in working memory, processed into executive systems, be subject to evaluation and judgment, and stored in memory.

Unconscious processes are believed to be more transient and evanescent, confined into peripheral modules in the brain. However, as demonstrated by growing experimental results, stimuli may still be processed quite deeply within the stimulus-related cognitive domain, even in the absence of consciousness. Thus, some features of emotions, numbers or words processing as semantic evaluation may be performed unconsciously, but also novelty detection, motivation or some aspect of executive functioning.

I.3. CAN CONSCIOUSNESS PERSIST DURING SLEEP?

From this brief review on neural signatures of consciousness and related cognitive processing, we can see that sleep embeds all the dimensions of consciousness, but that they do not systematically evolve together. Notably, while the level of consciousness appears to be reduced, some internal awareness may be preserved in dreams. The simple notion of sleep as a non-conscious state is then far to reflect the precise evolution of consciousness during sleep. Also, we just saw that changes in the level of consciousness have strong influences on the integration of sensory information across the brain and its cognitive processing.

Now we identified the neural signatures associated with consciousness, I will then proceed to the second step of our approach to better characterize sleep consciousness: inferring conscious states in evaluating the spontaneous activities during sleep with respect to the previously identified signatures of consciousness.

After having described subjective reports on external and internal awareness upon waking from each sleep stage, I will detail spontaneous physiological activations for each of them in first *i*) describing the modifications of arousal – in term of activations in the ascending activating system (brain stem – thalamus – cortex axis) –, and then *ii*) in analyzing how the signatures of consciousness are consequently impacted.

In this section, as I will describe spontaneous activities through sleep stages, I will only be able to infer from physiological activities the modifications in arousal and internal awareness. I will assess the signatures of consciousness in response to external stimuli in the following section.

I.3.1. Subjective report

I.3.1.1. Awareness of the environment

Decrease in awareness of the environment closely relates with the loss of responsiveness when falling sleep. Subjects feel progressively more and more distant from the environment, and report a complete loss of awareness of their surroundings only after having reached NREM2 sleep (Foulkes and Vogel 1965; Gibson et al. 1982; Bonnet and Moore 1982; Wackermann et al. 2002; Yang et al. 2010). The occurrence of the first spindles correlates with a rapid increase in thresholds of auditory perception and complete loss of awareness is reached in the subsequent few minutes.

Thus, it is important to note here that the classification of Rechtschaffen and Kales (1968) and the recent update from the AASM (2007), which define the start of sleep by the first epoch of NREM1, do not reflect the consciousness fading time point, which is better revealed by the first sleep spindle.

1.3.1.2. Oneiric content

Except in a few cases, where dream mentation incorporates sensory information from the environment (Hoelscher et al. 1981; Burton et al. 1988), dream content emerges from spontaneous activities of the sleeping brain. We can note here, however, that it has been a matter of debate whether dreams would be conscious *post-hoc* reconstructions more than perceptions built during sleep. Indeed, mental or oneiric content is obviously not reported during sleep, but is remembered after sleep, when waking up. Yet, recent evidence strongly suggests that perceptions are well experienced during sleep, from results on lucid dreamers (Voss et al. 2013) and the development of methods that enable the decoding of the content of dreams during sleep (Horikawa et al. 2013), results that I will develop below. For a long time, the way to study oneiric content has been to wake up subjects from the different sleep stages and collect the narrative dream content. Some dream mentation is reported from all sleep stages, but significantly differs in frequency and nature between stages.

1.3.1.2.1. NREM1 sleep

When woken up from NREM1 sleep, subjects report 80 to 90% vivid perceptions, often static and mostly visual as single snapshots, called hypnagogic hallucinations (Foulkes and Vogel 1965; Hori et al. 1994). Recently, Horikawa et al. (2013) used a machine learning classifier to decode the mental imagery of subjects during sleep onset. Their classifier was trained during waking on brain fMRI activations elicited by images of different semantic categories. When tested on fMRI activations during sleep, this classifier could significantly predict the mental imagery of subjects just before awakenings, as confirmed by subjects' reports after waking up. They could thus show that perceptions in sleep reported by subjects well correlated with sleeping brain activities.

1.3.1.2.2. NREM2 sleep and SWS

From NREM sleep, dreams reports fluctuate between 7 to 74% depending on studies (Dement and Kleitman 1957; Foulkes 1962; Rechtschaffen et al. 1963; Burton et al. 1988). Actually, higher rate were found when the question asked to subjects after awakening referred to 'thoughts' more than 'dreams', suggesting that oneiric content during NREM sleep is more logical and thought-like.

I.3.1.2.3. REM sleep

75 to 90% of awakenings from REM sleep produce vivid dream recall (Dement and Kleitman 1957; Foulkes 1962; Rechtschaffen et al. 1963; Burton et al. 1988). They are characterized by a complex scenario, often fantastic, illogical or absurd. Subjects experience rich sensory-motor perceptions, highly visual (olfactory and gustatory sensations are rarely perceived (Zadra et al. 1998)). Emotions are various and extremely intense, sometime even more vivid than during wakefulness. Finally, subjects dreaming experience cognitive defects, as lack of judgment or reduced voluntary control, executive functions and self-awareness (for reviews see Nir and Tononi 2010; Hobson 2010).

Exceptionally, volitional control and self-reflective awareness may be regained, in a particular dream state called lucid dream (Voss et al. 2013). Subjects become aware that they are dreaming and can control or change the scenario of the dream, still remaining deeply asleep. This regain in self-reflective awareness and cognitive control has been used to bring further evidence that dreamed perceptions are well experienced during sleep and not created upon waking. Dresler et al. (2011) asked subjects to perform a predefined motor sequence during sleep if they were able to reach lucid dreaming, and recorded related brain activities in fMRI and near-infrared spectroscopy. They showed that dreamed movements elicited activations in the sensorimotor cortex, confirming that dream perceptions are well experience during sleep.

I.3.2. Spontaneous activities and signatures of consciousness

We will here describe successively NREM and REM sleep, as they are subtended by very different activations in the ascending activating system (brain stem – thalamus – cortex) and in cortico-cortical networks, and in related signatures of consciousness.

I.3.2.1 NREM sleep

NREM sleep is characterized by the generation of several specific oscillations across brain regions, mostly synchronized with each other and which the main role as been associated with memory consolidation. After falling asleep, spindles and K-complexes first occur on a background of theta rhythms (NREM2), which slow down progressively in large slow oscillations (SWS). Each of those rhythms and oscillations reflects different states of brain activation.

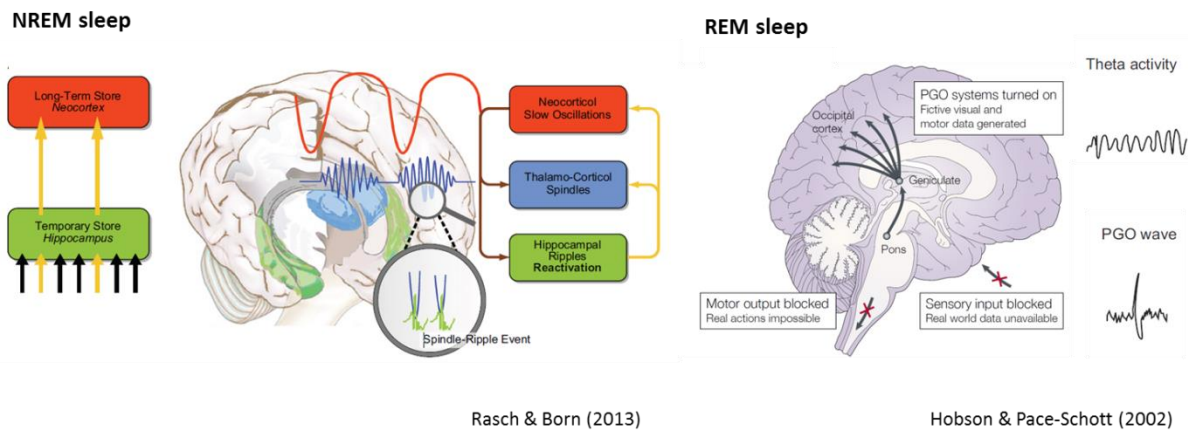


Figure 6. Genesis of endogenous activations

Left. In NREM sleep, sharp-wave ripples occur in the hippocampus, spindles in the thalamus and slow waves in the cortex. Ripples and spindles are synchronized with the UP phase of slow waves to transfer replayed memories from the hippocampus to the cortex.

Right. In REM sleep, Ponto-Geniculo-Occipital (PGO) waves are generated in the pons and are believed to generate mental imagery during dreams.

1.3.2.1.1. Shutdown of the ascending activating system

The transition from wakefulness to sleep is orchestrated by circadian and homeostatic pressures, which lead to the activation of the GABAergic neurons in the ventrolateral preoptic nucleus (VLPO) of the hypothalamus (Fort et al. 2009). This GABA activation inhibits excitatory neuromodulators in the brainstem ascending reticular activating system (ARAS) (acetylcholine, norepinephrine, serotonin and histamine) and in the hypothalamus (orexine), which project on the cortex. Thalamic activity switches from the tonic firing-mode of wakefulness to the burst firing-mode of sleep (Steriade et al. 1993b). Slow rhythms characteristic of NREM sleep then emerge from the liberation of thalamo-cortical networks from ascending activations. In addition to this ascending modulation, the cortex also regulates thalamic activity (McCormick 1992; Destexhe and Sejnowski 2002).

The inhibition of the ascending activation system has been shown in human studies on brain metabolism during sleep, which observed significant reductions in the brainstem, the thalamus and basal forebrain (Maquet et al. 1990; Maquet et al. 1997; Braun et al. 1997; Andersson et al. 1998; Kajimura et al. 1999; Kaufmann 2006).

At sleep onset, thalamo-cortical connectivity measured in fMRI has been shown to be strongly reduced (Spoormaker et al. 2010). Intracranial EEG recordings showed that the deactivation of the thalamus precedes for several minutes the deactivation of the cortical mantle (Magnin et al. 2010). Magnin and collaborators indeed showed with intracranial EEG recordings of epileptic patients that extensive cortical territories remain activated for several minutes (~10 min) after the thalamic deactivation. During this period, cortical areas progressively develop slow activities but, noteworthy,

with a great asynchrony between brain regions. Authors suggested that those persistent and topographically heterogeneous cortical activities, disconnected from the thalamus, may explain hypnagogic experiences characteristic of the wake–sleep transition. They may also explain why subjects still feel aware during NREM1 and overestimated by several minutes self-reported sleep latency with respect to the objective (polysomnographic) sleep onset (Bonnet and Moore 1982; Majer et al. 2007). This temporal dissociation between thalamic and cortical deactivations was also reported with fMRI (Kaufmann 2006). Interestingly, the opposite phenomenon was found during anesthesia (Velly et al. 2007), where the patient’s loss of consciousness was associated with strong deactivations of the cortical EEG several minutes *before* the deactivation of the thalamus. Also, still with intracranial recordings, Rey et al. (2007) showed that activation in the thalamus (measured by dimension of activation, which quantifies the amount of correlated information within a signal) was not different between NREM2 and SWS, whereas the cortical activity showed clear differences. The thalamus activity was then unable to account for the subtle changes in arousal and awareness during those two stages. Taken together, these results highlight the critical role of cortico-cortical connections on consciousness, and especially here on internal awareness.

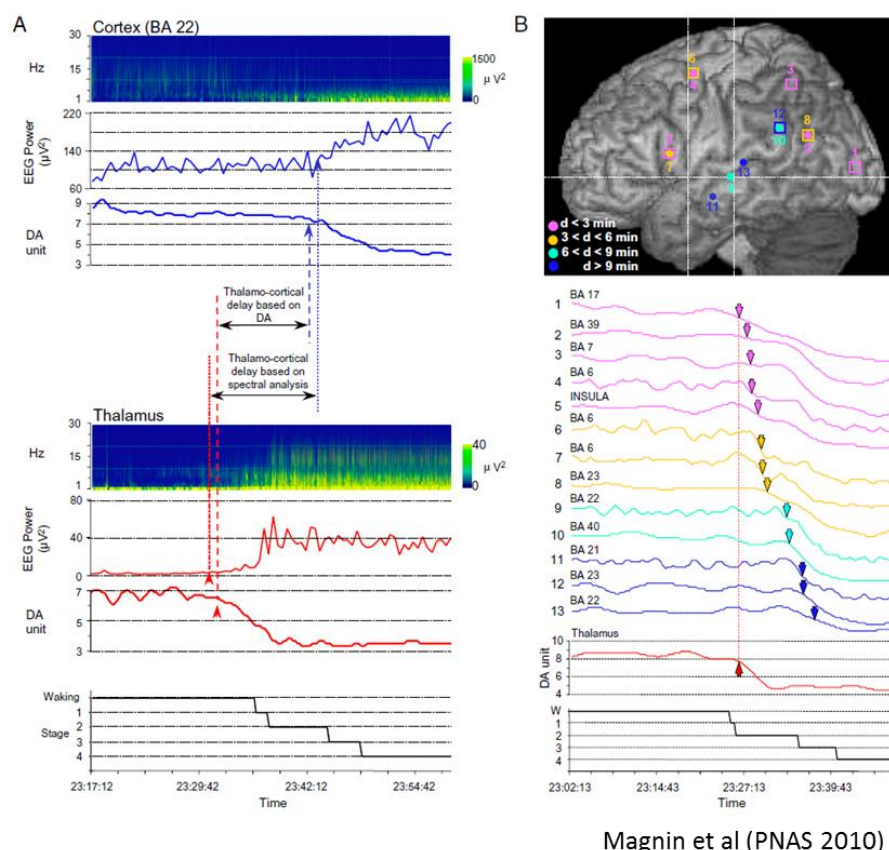


Figure 7. Thalamic deactivation at sleep onset

A. Dimension of activation decreases in the thalamus several minutes before the cortex.

B. Within the cortex, the deactivation of cortical areas is heterogeneous, with a delay of about 10 minutes between the different regions.

After the thalamo-cortical dissociation at sleep onset, a strong thalamo-cortical synchronization characterizes NREM sleep. Spindle oscillations are the first electrical marker of this thalamo-cortical synchronization. Single-unit recordings showed that they are generated in the reticular thalamus and result from rhythmic interactions between reticular and thalamo-cortical cells (Steriade et al. 1985). PET and fMRI studies in human indeed revealed strong correlations between thalamic activities and spindle oscillations (Hofle et al. 1997; Schabus et al. 2007; Dang-Vu et al. 2010; Caporro et al. 2012). At the cortical level, two types of sleep spindles oscillating at different frequencies are described: the slow spindles (~10–13 Hz) and the fast spindles (~13–18 Hz). The first are preferentially located in postero-central regions, and the second in frontal regions (Anderer et al. 2001; Schabus et al. 2007; Andrillon et al. 2011), with yet common related activities in the thalami, anterior cingulate, and insular cortices (Schabus et al. 2007; Caporro et al. 2012). They probably serve distinct functional roles, as fast spindles are more systematically related to memory consolidation than slow spindles (Rasch and Born 2013). Spindles, in recruiting the thalamo-cortical network in highly synchronized rhythms, are thought to block the transmission of sensory inputs to cortical areas (Steriade 1991; Dang-Vu et al. 2011). They have been suggested to strongly inhibit the cortical areas they rich (Peyrache et al. 2011). We saw that they indeed correlate with the fading of sensory awareness in the transition from wakefulness to sleep. An interesting clinical support for the absence of awareness during spindles, in addition to sleep studies, comes from absence seizures: the synchronous spikes-and-waves on scalp EEG typical of this seizure, which is associated with a sudden loss of awareness, have been proposed to origin from a ‘perversion’ or distortion of spindles oscillations (Gloor 1978; Kostopoulos 2000). These results then strengthen the role of thalamo-cortical synchronization in external awareness.

With the depth of sleep, the progressive increased hyperpolarization of thalamo-cortical cells lead to the generation of less spindles but increased delta rhythms (<4 Hz), characteristic of SWS (Steriade et al. 1993b). In the meanwhile, as we saw, responsiveness and awareness decrease (Rechtschaffen et al. 1966).

We see here that the inhibition of the ascending activating system during NREM sleep leads to the liberation of the spontaneous thalamo-cortical synchronization and slow oscillations. We will now describe how each signature of consciousness is consequently altered.

[I.3.2.1.2. Deactivation of the fronto-parietal network](#)

During NREM sleep global brain metabolism significantly decreases (Buchsbaum et al. 1989; Maquet et al. 1990; Nofzinger et al. 2002). The most affected regions at the cortical level are associative areas, i.e. prefrontal, parietal, anterior cingulate cortices and precuneus, in addition to subcortical structures involving the brainstem, the thalamus and basal forebrain (Maquet et al. 1990;

Maquet et al. 1997; Braun et al. 1997; Andersson et al. 1998; Kajimura et al. 1999; Kaufmann 2006). Sensory-motor areas are in comparison relatively preserved.

On scalp EEG in SWS, delta activity and slow waves are predominantly recorded in frontal sites (Finelli et al. 2001). Few PET studies aimed at analyzing changes in regional cerebral blood flow (rCBF) during those rhythms compared to wakefulness, and found that delta power was negatively correlated with rCBF in the medial frontal cortex, the orbitofrontal cortex, the anterior cingulate gyrus, the anterior part of the insula, the precuneus, as well as the basal forebrain, anterior hypothalamus, and the striatum (Maquet et al. 1997; Hofle et al. 1997; Dang-Vu et al. 2005).

These results, which overlap in part, suggest that the main brain areas involved in consciousness are strongly inhibited during NREM sleep.

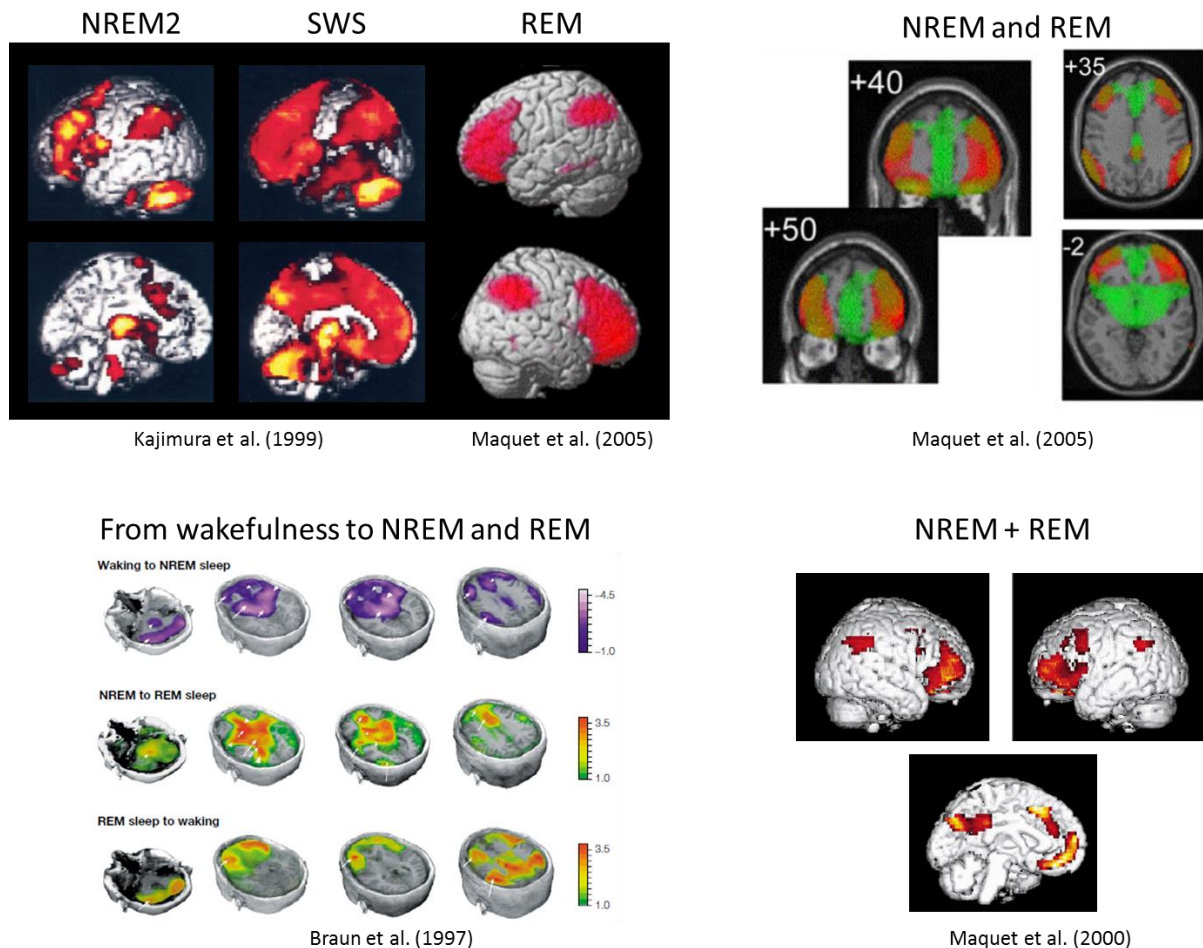


Figure 8. Decrease of cerebral blood flow in the different sleep stages

Top-Left. Regional deactivations in NREM2, SWS and REM sleep.

Top-Right. Decreased cerebral blood flow for SWS sleep (green) and REM sleep (red). Common deactivations in orange. In all sleep stages, parietal and dorsolateral prefrontal cortices are systematically deactivated.

Bottom-Left. Evolution of cerebral blood flow from wakefulness to NREM to REM sleep.

Bottom -Right. Decreased regional cerebral blood flow for both sleep stages combined.

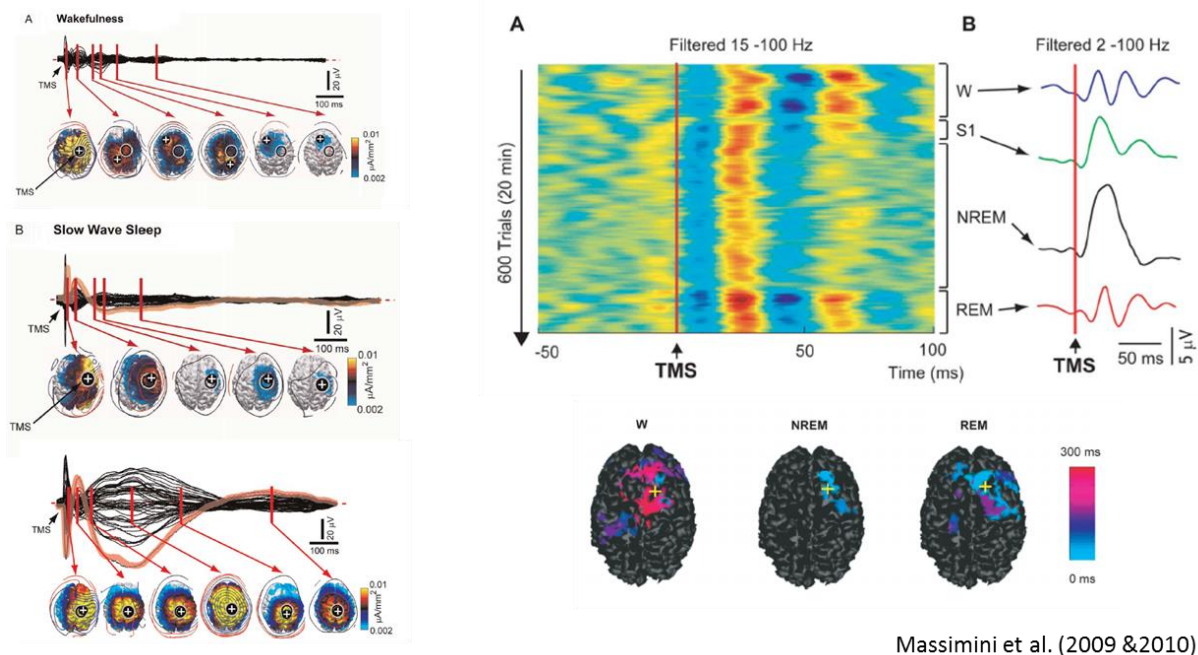
1.3.2.1.3. Decreased global information sharing

In addition to specific deactivations of key areas in the brain, cortical connectivity has been shown to strongly decrease during NREM sleep, preventing long distance information sharing.

Connectivity measures in fMRI revealed an increased modularity in NREM2 (Spoormaker et al. 2010; Boly et al. 2012; Tagliazucchi et al. 2013b), followed by a clear drop in connectivity during SWS (Spoormaker et al. 2010; Samann et al. 2011; Boly et al. 2012; Tagliazucchi et al. 2013b). Noteworthy, the disconnection was stronger for prefrontal and posterior cingulate cortices (Horovitz et al. 2009; Samann et al. 2011). Intracranial EEG recordings in epileptic patients also showed that cortical dimension of activation was significantly decreased in NREM sleep (NREM2 and SWS) compared to wakefulness (Rey et al. 2007; Magnin et al. 2010), and a decreased local and long-range gamma EEG coherence within cortical regions (Cantero et al. 2004). Finally, Massimini et al. (2005) assessed the information integration of the brain in measuring the EEG cortical reactivity to a pulse of TMS. During SWS, when the pulse was sent over lateral cortical regions, TMS evoked-responses were transient and localized to the stimulation site. Distant cortical areas ceased to be causally affected by the initial perturbation, suggesting a break-down in cortical integration. When the pulse was sent over centro-parietal regions, TMS triggered a stereotypical response of large amplitude, spreading over the cortex (Massimini et al. 2007), suggesting here a loss of cortical differentiation.

Beyond this global view on connectivity, what happens specifically during slow waves? During SWS, delta oscillations can be divided in two different oscillations arising from two different brain systems (Steriade et al. 1993b). Delta rhythms (<4 Hz) result, as sleep spindles, in the increased hyperpolarization of thalamo-cortical cells with the depth of sleep. Slow oscillations (<1 Hz) however, as K-complexes, are generated in the neocortex (Steriade et al. 1993c). They reflect oscillations of cortical neurons between UP (activated) and DOWN (deactivated) states, highly synchronized across the cortex via cortico-cortical connections. Actually, whereas cortical cells (as the thalamo-cortical neurons and the thalamic reticular nucleus) are silent during DOWN states, they fire at a frequency level very similar to wakefulness, in the beta-gamma range, during UP states (Steriade et al. 1996; Destexhe et al. 2007; Le Van Quyen et al. 2010). The slow cortical synchronization between UP and DOWN states is powerful enough to have as a consequence the grouping of the other rhythms (delta oscillations, thalamic spindles and hippocampal ripples) within its frequency range (Contreras and Steriade 1995; Mölle et al. 2002). In humans, an enhanced cortical coherence in slow-oscillatory, delta, slow-spindle, and gamma bands has also been shown during the UP states after learning (Molle 2004). Actually, the replay of previously learnt memories has been shown in animals to occur in the hippocampus, at a much faster rate than during wakefulness (20-times), within ripple events (Lee and Wilson 2002; Ji and Wilson 2007), and to be transmitted to the cortex through the synchronization of ripple events within thalamo-cortical spindles, occurring during the UP state of slow oscillations. In support to animal electrophysiological findings, hippocampal reactivations have been suggested in a

human PET study during SWS after a virtual navigation task; crucially, the size of the hippocampal reactivation during SWS was correlated to performance after sleep (Peigneux et al. 2004). Now, a significant number of studies could demonstrated a strong link between slow oscillations (and associated rhythms) and learning performances (Huber et al. 2004; Marshall et al. 2006; Mölle et al. 2009; Ngo et al. 2013). To summarize, during the UP states of slow waves, a strongly activated hippocampo-cortical network takes place, highly involved in memory consolidation.



Massimini et al. (2009 & 2010)

Figure 9. Cortical responses to TMS pulses in sleep

Left. During SWS, TMS pulses evoke slow waves that are either local or global and non-specific depending on stimulation site.

Right. TMS-evoked responses across sleep stages. During REM, the initial potential is similar to wakefulness.

Slow waves also exhibit a specific pattern of activation at the cortico-cortical level. In an interesting fMRI study, Dang-Vu and collaborators (2008) analyzed brain activities during slow oscillations compared to baseline (i.e. theta, alpha and beta activity during NREM sleep), and not compared to wakefulness as previous PET studies. They showed that slow oscillations were associated with significant *increases* in brain activity in the inferior frontal gyrus, middle frontal gyrus, precuneus, posterior cingulate cortex, parahippocampal gyrus, midbrain, pontine tegmentum, and cerebellum. Noteworthy, no decrease in activity was observed. Recent studies using high-density EEG source modeling, which have the strong advantage to have enough temporal resolution to differentiate

UP and DOWN states, showed that slow waves were actually associated with activations traveling across the cortex following an antero-posterior axis (Massimini et al. 2004). More precisely, activations were found in the medial frontal gyrus, the middle frontal gyrus, the inferior frontal gyrus, the anterior cingulate, the precuneus, and the posterior cingulate (Murphy et al. 2009). Those activated regions confirm previous results and have been interpreted as the preferential propagation sites for slow waves, which interestingly correspond to parts of the brain structural connectivity matrix (Massimini et al. 2004). Noteworthy, those structural core regions shape the default mode network, which may explain why parts of it have been found preserved during early sleep (Horowitz et al. 2008; Murphy et al. 2009; Larson-Prior et al. 2009) or even deep sleep (Tagliazucchi et al. 2013a). The notion that slow waves during deep sleep spread over the structural connectivity network is in line with recent results in anesthesia (Bartfeld et al. 2015), which showed that the functional connectivity pattern during deep sedation faithfully reflected the structure of anatomical connectivity. These stereotypical activations across the structural matrix are then less susceptible to contain a differentiated information, and lead to conscious percepts (Tononi 2004).

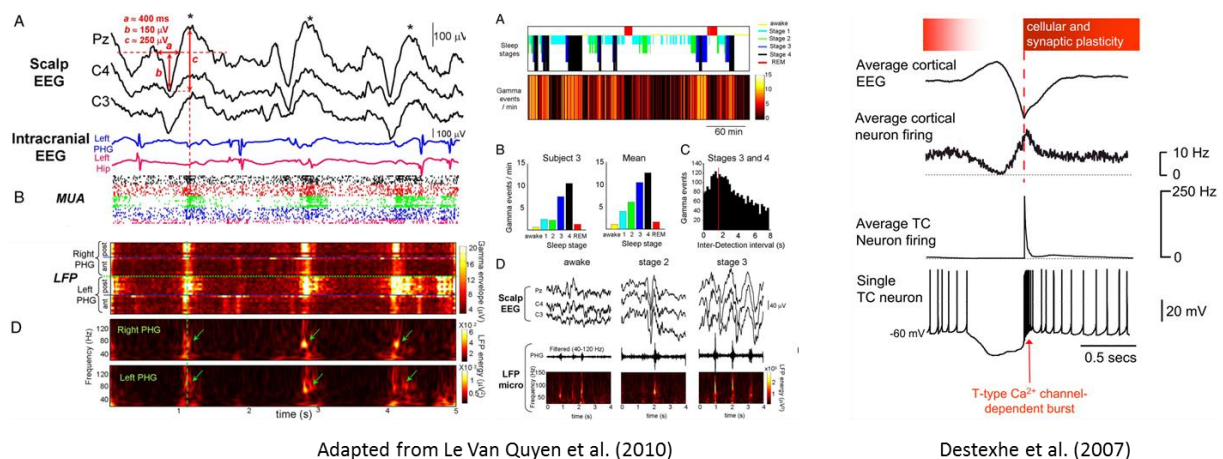


Figure 10. Gamma oscillations occur during the UP states of slow waves

Left. Gamma activity in the para-hippocampal gyrus (PHG) during the UP states.
 Middle. Gamma activity in the PHG depending on sleep stages.
 Right. Gamma activity in thalamo-cortical neurons during the UP states.

I.3.2.1.4. Not distributed but local sleep

Growing evidence suggests that sleep is not a global and homogenous phenomenon, but is rather local in nature. Krueger et al. (2008) suggested that sleep is a fundamental property of neuronal assemblies, which emerge locally at the cortical column level in function of its local homeostasis. We

already showed in previous results the increased modularity of the sleeping brain and regional metabolic modulations. Evidence for local sleep is strengthened by electrophysiological observations of high spatial resolution in animals, healthy humans and in sleep disorders, which show clear spatial dissociations between activations and slow rhythms, and blurs the limits between sleep and wakefulness.

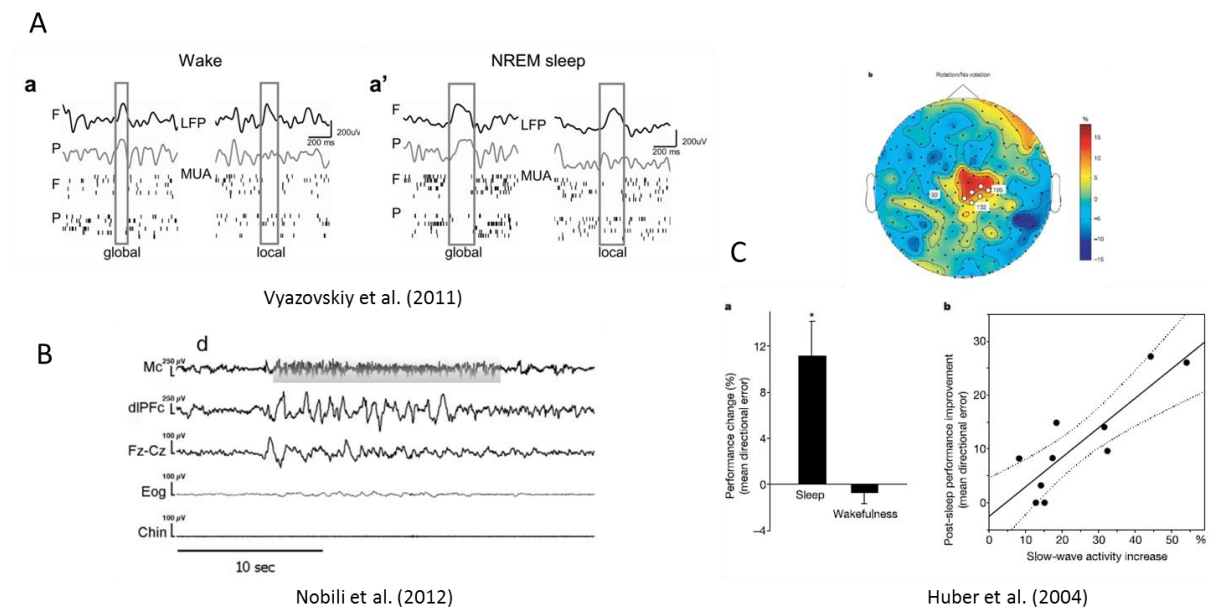


Figure 11. Local sleep

A. Left. Local sleep in awake rats. OFF periods can be global across the cortex or local (F:frontal cortex; P:parietal cortex). Right. Local sleep in sleepy rats. During NREM sleep, OFF periods can also be global or local.

B. Local activations in the human motor cortex during NREM sleep in intracranial EEG.

C. Local increase in slow wave activity in NREM sleep following a motor target detection task. Performances are increased after a sleep period compared to a period of wakefulness, and are positively correlated with slow wave activity.

During wakefulness, local sleep patterns can be recorded in the brain. Marine mammals exhibit unilateral hemispheric slow waves (Mukhametov et al. 1977; Lyamin et al. 2008), conferring to the animal the surprising status of being half awake, half asleep, while still swimming. In rats, increased sleep pressure lead to the emergence of OFF-periods associated with slow waves in local cortical areas (Vyazovskiy et al. 2011), while the animal still behaves as awake. This local sleep increases with the time awake and leads to a decrease in performances. The same observation was seen in monkeys, in which burst-pause pattern of sleep in V4 was detected while the monkey was still performing a visual task (Pigarev et al. 1997). In humans, auditory and visuomotor tasks lead to

increased theta power in related regions during wakefulness, which was correlated to slow wave activity during subsequent sleep in the same areas (Hung et al. 2013).

In the transition to sleep, we saw that cortical areas in humans shutdown progressively through the cortical mantle, in an heterogeneous manner in time and space (Kaufmann 2006; Magnin et al. 2010). Still with intracranial recordings, Nobili et al. (2012) revealed that while one patient was behaviorally awake, 10 minutes before sleep, slow oscillations were already recorded in the thalamus and sleep spindles in the hippocampus.

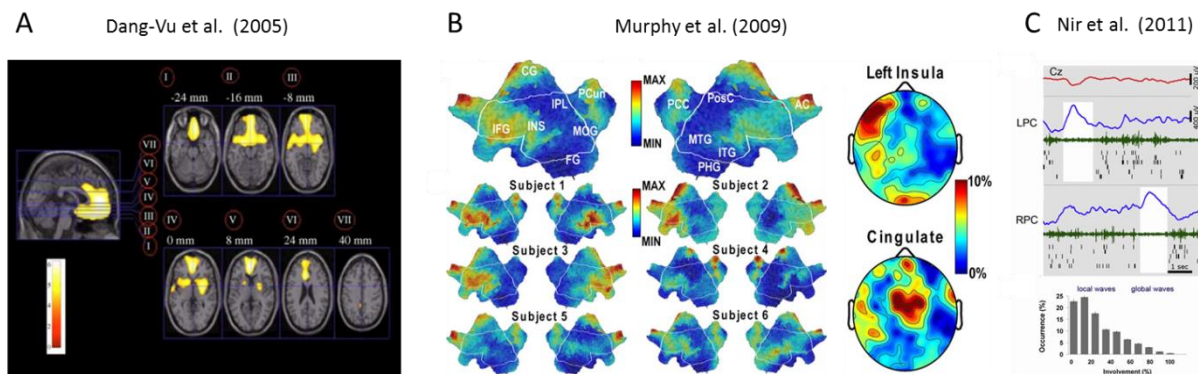


Figure 12. Slow waves are local events that propagate preferentially in regions of the default network

A. Correlations between regional cerebral blood flow (rCBF) and delta power (1.5– 4 Hz) spectral density. Delta power predominates in frontal regions.

B. Left. Source modeling of slow waves from hd-EEG, cortical flat map displaying for all waves the total involvement of each voxel. Hot spots can vary between subjects, but the same areas are highly involved in all subjects: the anterior cingulate, the cingulate, the posterior cingulate, the precuneus, and the left inferior frontal gyrus and insula. Right. Scalp origins of waves that originate in either the left insula or the cingulate gyrus (left).

C. Local slow waves, here localized either to the left prefrontal cortex or to the right prefrontal cortex, with below the percentage of occurrence of local versus global slow waves.

During sleep, sleep patterns also exhibit local modulations, in function of previous activity or learning. High density EEG and intracranial recordings showed that individual slow waves emerge from distinct cortical areas and propagates across unique subsets of cortical structures and are thus definitely more local than global (Murphy et al. 2009; Nir et al. 2011). Moreover, they are locally modulated in cortical areas in function of their previous recruitment during encoding (Cantero et al. 2002; Huber et al. 2004; Huber et al. 2006). Activation enhancement in fMRI during NREM sleep is in the same way region specific, function of the task performed during wakefulness (Yotsumoto et al. 2009). Sleep spindles also show local patterns, as demonstrated for slow and fast spindles (Schabus et

al. 2007; Dehghani et al. 2010; Andrillon et al. 2011). Finally, local cortical reactivations are observed during sleep, as in the motor cortex during NREM sleep (Nobili et al. 2012).

To the end, activated coherent networks as the hippocampo-cortical ones during replay (Ji and Wilson 2007; Wierzynski et al. 2009; Logothetis et al. 2012), may be too localized at the cortical level so that they do not generate the global workspace ignition and information broadcasting also necessary for consciousness. In addition, the hippocampo-cortical replay may prevent encoding of representations to occur, which need the transfer of information from the cortex to the hippocampus, and then prevent the recall of potential representations after waking-up. These localized patterns of activations and reversed hippocampo-cortical activations may then explain why dreams are rarely reported from SWS. The rare oneiric activity during SWS may emerge when slow waves propagation is strong enough for the global broadcasting and encoding to occur, despite we saw that the activation during slow waves is quite stereotyped and may not contained enough differentiated information. Alternatively, and maybe more probably, dreams may emerge from more sustained activations in other loco-regional networks, as it happens in parasomnia.

Indeed, an excessive local sleep is the manifestation of sleep disorders as parasomnia. During sleepwalking, patients exhibit the striking dissociation of having motor behavior during deep sleep, with highly emotional dreams (often intense nightmares and hallucinations). Scalp EEG is characterized by a dissociation between high-amplitude slow waves in anterior areas and alpha and beta rhythms in posterior ones (Schenck et al. 1998; Zadra et al. 2004). Those observations have recently been confirmed with intracranial EEG in one epileptic patient with parasomnia, which showed increased delta activity in fronto-parietal associative cortices along with local activations in the motor and cingulate cortices (Terzaghi et al. 2009). Those data also strengthen the role of fast oscillations and the fronto-parietal network in consciousness.

[I.3.2.1.5. Late and sustained activations?](#)

In addition to the local pattern of slow waves, the alternating activation-deactivation may not provide enough time for sustained activations to occur during UP states, thus preventing consciousness to emerge. Apart in SWS, there is no evidence from spontaneous activations supporting that sustained activations would be disrupted.

[I.3.2.1.6. Top-down activations?](#)

Considering top-down activations, no direct experimental evidence has been provided either for their presence or for their absence during sleep. Only speculations have been advanced for explaining dream mentation. Some authors consider dream as bottom-up processes emerging from the brainstem, mainly occurring in REM sleep (Hobson and Pace-Schott 2002; Hobson 2010). Others highlight the fact that dreaming can occur in all sleep stages and believe that dreams are, as mental imagery, subtended by top-down activations (Nir and Tononi 2010; William Domhoff 2011; Foulkes

and Domhoff 2014). Evidence for this last view comes from lesions studies of dreaming, which show that complete cessation of dreaming is mainly associated with damages in the temporo-parieto-occipital junction (Murri et al. 1985; Solms 2000), also involved in mental imagery (Kosslyn 1980). In addition, we note that this region has also been involved in hallucinations in schizophrenic patients (Jardri et al. 2011; Mondino et al. 2015). Another evidence comes from disabled patients, such as those with congenital paraplegia that yet dream of walking (Saurat et al. 2011), then strongly suggesting top-down activations during sleep.

SUMMARY OF THE KEY POINTS

NREM sleep is characterized by the inhibition of the ascending activating system, which leads to the hyperpolarization and synchrony of thalamo-cortical networks and the emergence of slow cortical rhythms. This results in a global decrease in brain metabolism.

At the cortical level, along with slow oscillations, we observe significant changes in activity that may be responsible for the loss of consciousness:

- A predominant deactivations of hyper-associative areas such as the prefrontal network
- A breakdown in long-range cortico-cortical connectivity with increased modularity
- Mainly local processes whose activities are function of previous discharge during wakefulness and local homeostasis.

However, activations are still found:

- During UP states of slow waves, in which increased activities in gamma frequency range are as high as during wakefulness, and during which the hippocampo-thalamo-cortical replay occurs
- In parts of the default mode network where slow waves activations spread, probably reflecting fundamental activities of the structural core.

These activities may then lead to the emergence of basic forms of internal awareness, but in most of the cases, we hypothesize that the hippocampal replay may prevent those internal representations from being encoded in memory.

I.3.1.2. REM sleep

After NREM sleep, the brain switches to very different rhythms and activations. Theta and alpha rhythms are predominant and trains of rapid eye movements (REMs) occur (phasic REM) in the context of a general body atonia.

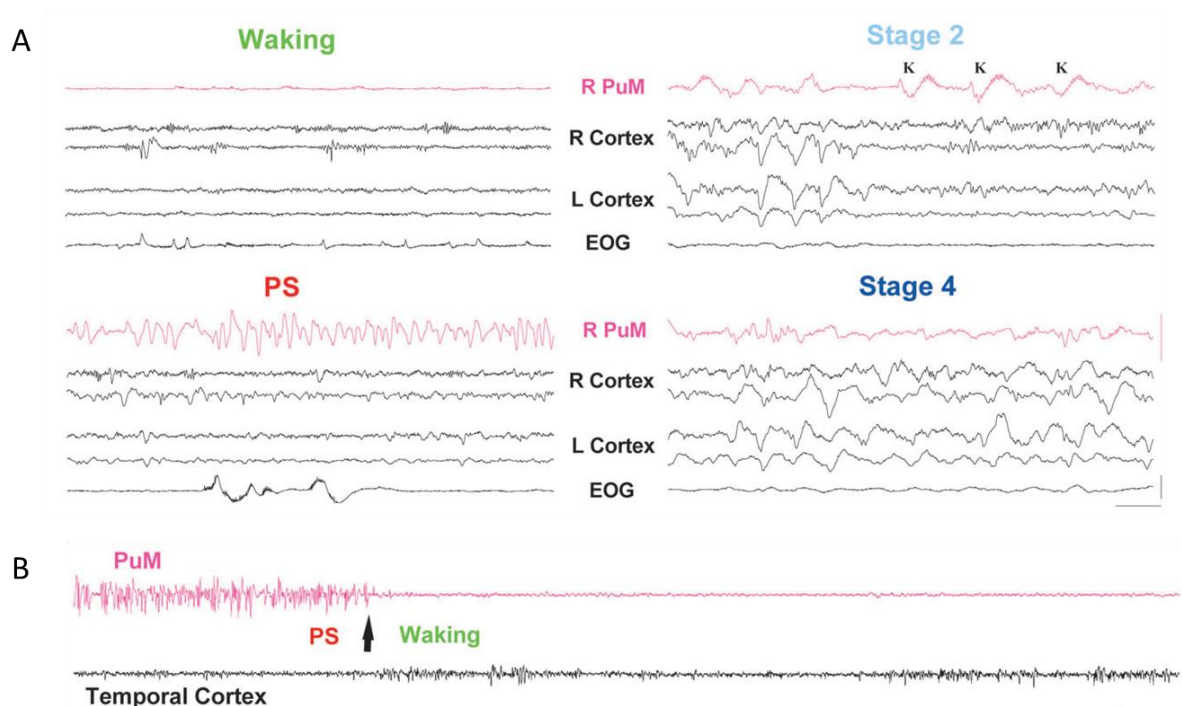
I.3.1.2.1. Partial reactivation of the ascending activating system

REM sleep is generated within the brainstem (Jouvet 1962), where cholinergic projections are reactivated. Under acetylcholine modulation, thalamic cells switch from the slow burst firing mode of NREM sleep to the tonic mode typical of wakefulness, leading to sustained high frequency (30-40 Hz) oscillations in thalamo-cortical loops and then to cortical reactivation (Steriade et al. 1993a; Steriade 1997). In the meanwhile inhibitory projections to spinal motoneurons generate atonia.

If high frequency activations occur in thalamo-cortical networks and theta and alpha oscillations are recorded at the scalp level as in quite wakefulness, we may then ask why we are still deeply asleep and unconscious from the external world during REM sleep.

One first hypothesis is that the brain becomes engaged in strong close thalamo-cortical loops of sustained intrinsic neuronal activity and is then disconnected from the environment (Linás and Paré 1991). Sensory cortices have indeed been shown to be less reactive to external inputs during phasic REM sleep (Sallinen et al. 1996; Takahara et al. 2002; Wehrle et al. 2007), when REMs occur, which is characterized by stronger thalamo-cortical activations (Wehrle et al. 2007).

Also, Magnin et al. (2004) recently demonstrated with intracranial recordings in humans that the whole thalamus is actually not activated as if awake: the medial pulvinar nucleus exhibits slow wave activity as if deeply asleep. The pulvinar constitutes one of these higher-order relays of the thalamus, which is involved in transferring information between associative cortical areas (in opposition to first-order relays, as lateral geniculate nuclei that transfer sensory information from retina to primary cortices) (Shipp 2003; Sherman 2007). As the authors note, the medial pulvinar is densely connected to important associative areas, and especially the posterior cingulate cortex, the parietal cortex and the dorsolateral prefrontal cortex, areas which are part of the rare regions deactivated during REM sleep (Maquet et al. 1996; Maquet 2000). The persistence of slow oscillations in this nucleus may be explained by the weak cholinergic inputs that it receives from the brain stem (Hirai and Jones 1989).



Adapted from Magnin et al. (2004)

Figure 13. Delta oscillations in the medial pulvinar nucleus (PuM) of the thalamus during REM sleep

- A. PuM and cortical activities in the different states of vigilance. During REM sleep, the PuM present delta oscillations while the cortex present high frequency rhythms.
 B. Transition between REM sleep and wakefulness: abrupt disappearance of delta oscillations.

Selective modulation of intra-thalamic activations, with specific deactivation of higher-order nuclei as the medial pulvinar, would then prevent information sharing across the fronto-parietal network, key regions associated with cognitive control and consciousness. This may explain the loss of some executive functions during dreams as volitional control and metacognition, and may also be responsible of the loss of awareness of external stimulation.

In addition to the regain in acetylcholine modulation, specific activations originating from the brainstem also participate in the generation of endogenous activations. At the electrophysiological level, a hallmark of REM sleep rhythms are the so-called ponto-geniculo-occipital (PGO) waves, sharp field potentials associated with rapid eye movements (REMs) and recorded primarily in animals and especially in cats (Jouvet et al. 1959; Brooks and Bizzi 1963; Bizzi and Brooks 1963). First believed as a specific mark of REM sleep, they actually occur similarly during wakefulness during eye movements (Brooks 1968a). PGO waves originate in the pontine reticular formation and propagate in the lateral geniculate nucleus of the thalamus to occipital cortices. They occur before and during each REM, are lateralized according to eye movement direction and may serve to convey eye movement

information to visual cortices (Nelson et al. 1983) and create visual imagery of dreams (Hobson and McCarley 1977). Also, PGO waves are not restricted to visual cortices, but can be recorded in several brain regions across the cortex (Brooks 1968b). They occur in synchrony with hippocampal theta oscillations (Karashima et al. 2005; Karashima et al. 2007) and are thought to promote synaptic plasticity in the region they reach, contributing to brain maturation (Davenne et al. 1989; Shaffery et al. 1999) and memory consolidation (Datta 2000; Mavanji and Datta 2003; Datta et al. 2004) during sleep.

In humans, PGO waves could not be strictly defined, as direct pontine and geniculate recording cannot easily be performed. To my knowledge, only one study recently reported pontine field potentials similar to PGO waves in one patient implanted for Parkinson's Disease, which were localized near the ponto-mesencephalic tegmentum and were followed by subsequent cortical potentials after 20 to 140 ms (Lim et al. 2007). Otherwise, neuroimaging studies can indirectly assess the presence of PGO waves in humans in analyzing brain activations associated with REMs. Accumulating evidence supports PGO waves-equivalent in humans, with activations of brain networks very similar to the ones reported in animals: activations were found almost systematically in the pontine tegmentum, the thalamus and the visual cortex, with associated activations in premotor areas (frontal eye field, supplementary motor area) and in the limbic network (parahippocampal gyrus, amygdala, anterior cingulate) (Hong et al. 1995; Ioannides 2004; Miyauchi et al. 2008; Peigneux et al. 2001b; Wehrle et al. 2005), but also in non-visual cortices, as in the motor cortex and language areas (Hong et al. 2009).

More precisely, a recent study has just brought new insights to the description of cortical activities time-locked to REMs (Andrillon et al. 2015). EEG cortical potentials related to REMs were first described a long time ago (McCarley et al. 1983), but thanks to intracranial recordings in epileptic patients, authors showed that REMs during REM sleep were associated with a pattern of activation (decreased firing-rate just before REM onset and increased firing-rate immediately after) in the neocortex and the medial temporal lobe strongly similar to that in wakefulness, in the presence of REMs and after visual stimulation. They suggested that those cortical activations may represent PGO waves, and that "REMs during sleep rearrange discrete epochs of visual-like processing as during wakefulness". These results may support the 'scanning hypothesis', which postulate that REMs during sleep scan the visual scene (Arnulf 2011). However, whether REMs are involved in scanning or in the generation of dream imagery (or maybe the both) is still a matter of debate. In any case, we conclude from these studies that activations very similar to wakefulness occur during REM sleep, and especially phasic REM sleep.

I.3.1.2.2. Distributed activations without the fronto-parietal network

Globally, the brain metabolism increases in REM sleep to a similar level to that of wakefulness (Buchsbaum et al. 1989; Maquet et al. 1990; Braun et al. 1997). However, it exhibits a much more heterogeneous pattern of activations. On one hand, the brainstem, thalamus and basal forebrain are reactivated, along with limbic and paralimbic areas (amygdala, parahippocampal gyrus, anterior cingulate cortex, orbital and medial prefrontal cortex), which can show a level of activation even superior to wakefulness (Maquet et al. 1996; Braun et al. 1997; Nofzinger et al. 1997). This may explain the highly emotional nature of dreams during REM sleep.

On the other hand, as we saw, the dorsolateral prefrontal cortex, parietal cortex, posterior cingulate gyrus and precuneus remain deactivated (Maquet et al. 1996; Braun et al. 1997; Nofzinger et al. 1997), regions that are precisely involved in consciousness.

Interestingly, as in NREM sleep, REM regional brain activity can be modulated by prior learning, reinforcing the contribution of REM sleep in memory consolidation (Maquet et al. 2000; Laureys et al. 2001; Peigneux et al. 2003).

I.3.1.2.3. Partial regain of information sharing

During REM sleep, cortical connectivity may be partially recovered compared to NREM sleep. EEG coherent activity was found increased within perceptual regions, despite decreased between frontal and perceptual region (Corsi-Cabrera et al. 2003). Interestingly, trans-callosal inhibition seen in wakefulness by TMS was found strongly decreased after awakening from REM sleep, suggesting a modification in intrahemispheric connectivity in REM sleep (Bertini et al. 2004). Still using TMS, Massimini et al. (2010) showed that TMS pulses elicited early fast oscillations similar to wakefulness, before vanishing as in NREM sleep, suggesting that effective connectivity may be partially restored.

In term of synchrony, Llinas and Ribary first described in REM sleep widespread, coherent spontaneous 40-Hz oscillations as in wakefulness over the scalp EEG (Llinas and Ribary 1993). These results were further infirmed by intracranial EEG data which showed decrease local and long-range gamma EEG coherence within cortical regions in humans (Cantero et al. 2004), as well as in rats (Cavelli et al. 2015) and cats (Castro et al. 2013). However, when analyzing separately tonic and phasic REM sleep, studies showed increased gamma range connectivity only during phasic REM (during REMs), both within the cortex (Brankačk et al. 2012) and the hippocampus (Montgomery et al. 2008).

Also, interestingly, increased frontal 40 Hz coherence was recorded during episodes of lucid dreaming compared to classic REM sleep, with similar levels to wakefulness (Voss et al. 2009). And

in an even more convincing experiment, Voss and collaborators increased lucid dreaming in applying transcranial stimulation in low-gamma frequency range (25-40 Hz) over fronto-temporal sites (Voss et al. 2014), while stimulation at other frequencies had no effect. Thus, they causally linked high frequency oscillations in fronto-temporal regions with the regain of self-awareness and metaconsciousness during sleep. Moreover, prefrontal cortices (middle and superior gyrus) have been shown to be strongly activated during lucid dream compared to non-lucid REM sleep in fMRI (Dresler et al. 2012), in association to parietal lobules, precuneus, cuneus and occipito-temporal cortices. A recent study also reported greater grey matter volume in the frontopolar cortex (BA9/BA10) in high lucid dreamers compared to rare lucid-dreamers (Filevich et al. 2015), suggesting shared neural systems between lucid dreaming and metacognitive functions, believed to be located in those anterior frontal areas. These results on lucid dreaming highlight the role of frontal areas in metaconsciousness, and reveal that high-level of information integration for endogenous stimuli can occur without the regain of external awareness.

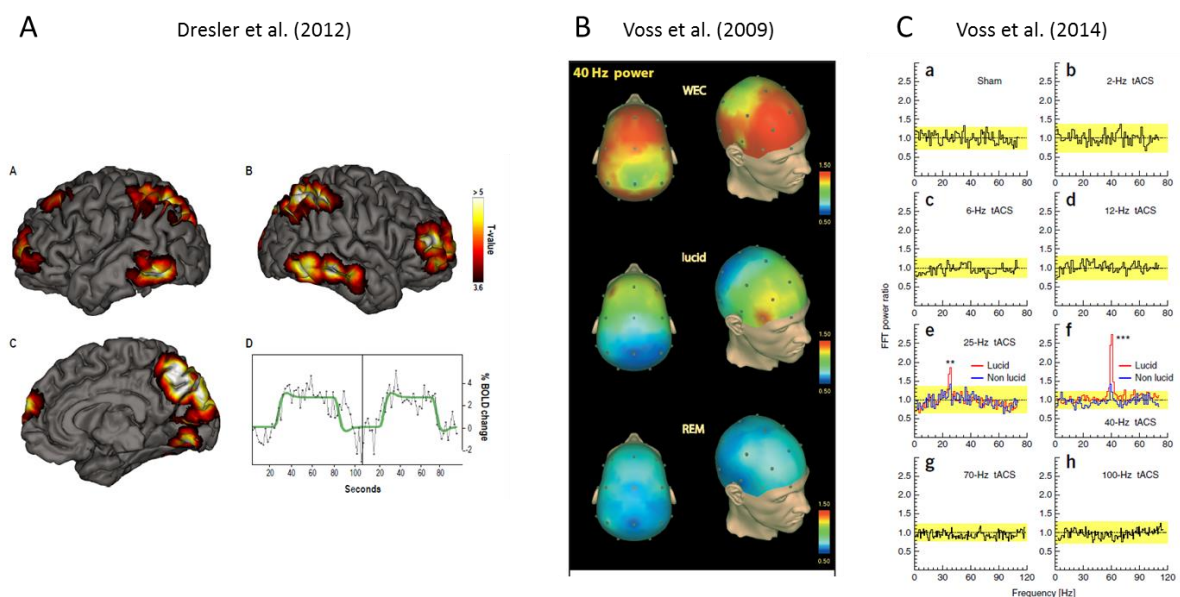


Figure 14. Lucid dreaming

A. Areas significantly activated during lucid epochs in REM sleep ($pFDR < 0.005$) in fMRI, compared to non-lucid REM sleep: bilateral precuneus, cuneus, parietal lobules, and prefrontal and occipito-temporal cortices are activated.

B. 40 Hz activity increases in anterior areas during lucid dreaming. Single subject γ 40-Hz standardized current source densities power during wakefulness (top), lucid dreaming (middle), and REM sleep (bottom).

C. Fronto-temporal tACS stimulation at 25 and 40 Hz induces lucid dreaming. FFT power ratios of activity during versus activity before stimulation for the different stimulation conditions: with 40-Hz and 25-Hz stimulation, lucid dreams (red line) are accompanied by a significantly larger increase in the respective frequency band than non-lucid dreams (blue line).

I.3.1.2.2. Late, sustained, and top-down activations?

Considering those signatures, the same remarks are done than for NREM sleep. However, the higher frequency of dreaming and the existence of lucid dreaming, which is believed to emerge only from REM sleep, highly suggest the presence of top-down processes in this stage.

SUMMARY OF THE KEY POINTS

REM sleep is characterized by the partial reactivation of the ascending activating system. The regain in acetylcholine modulation lead to:

- A reactivation of the thalamo-cortical network with activations similar to wakefulness in the gamma frequency range
- A reactivation of cortical areas, such as sensory motor cortices and the limbic cortex, also with activations in the gamma range
- A global metabolism as high as during wakefulness.

However, this regain in activation is not homogeneous:

- Parts of the thalamus remain deactivated, such as the pulvinar.
- Specific brain areas remain deactivated, such as the dorsolateral prefrontal cortex, parietal cortex and precuneus.

Those activity changes may explain the regain in highly emotional forms of internal awareness, but which misses some features of waking consciousness believed to be subtended by prefrontal and precuneus regions, as volition and self-awareness. Yet, in some cases,

- Activations and high beta-gamma frequencies may be recovered in the prefrontal cortex, parietal cortex and precuneus, in association to the regain in self-awareness and volitional control during lucid dreaming.

I.4. PROCESSING OF EXTERNAL STIMULI DURING SLEEP

The sleeping brain is strongly engaged in processing internal stimuli. In consequence, how does the sleeping brain react to external stimulations? Do external stimuli reach sensory cortices? How far are they processed? I will review here the current findings before introducing my own work.

I.4.1. Behavioral responsiveness

Responsiveness to external stimuli significantly decreases when falling asleep during NREM1 and remains strongly reduced through following sleep stages. When falling asleep, subjects are still able to perform simple tasks, despite increased error rates, reaction times and misses (Ogilvie and Wilkinson 1984; Ogilvie et al. 1989; Hori et al. 1994; Casagrande et al. 1997). This behavioral slowdown is progressive through NREM1 and last emitted responses can be observed until the emergence of the first sleep spindles. After a few minutes of NREM2, generally no overt oriented motor reaction is collected anymore and responsiveness is measured via micro-arousal and awakening reactions thresholds. We can note that in addition to cortical arousals, autonomic micro-arousals as increase in heart beat can be observed without any acceleration in EEG rhythms (Halász et al. 2004). Awakening thresholds are significantly increased during NREM2, SWS and REM sleep, but the higher ones are observed during SWS (Rechtschaffen et al. 1966). In SWS the sleeper is indeed very hard to wake up and is often confused after waking.

Noteworthy, some studies that used intense training in behavioral tasks could describe some motor responses during sleep. Williams et al. (1966) trained subjects during several nights to respond to tones and could observe motor responses, mainly in NREM2 or REM, even in the absence of cortical arousal on scalp EEG. Burton et al. (1988) trained subjects to take a deep breath in response to tones, and found high levels of behavioral responses in NREM2 and REM sleep. Interestingly, the response rate was the highest (around 80%) when subjects did not report any dream mentation before waking up, and decreased when subjects did report dream mentation related or not to presented sounds (around 50%). They then suggested that reduced responsiveness to external stimuli was at least in part due to ongoing internally-generated mental activity during sleep.

These studies show that in most cases responsiveness is lost after the first minutes of NREM2 sleep. However, after intense training, oriented behavioral responses may be emitted during sleep. We will see below that a recent EEG study (Kouider et al. 2014) could show motor-preparation potentials during sleep, in line with those last results.

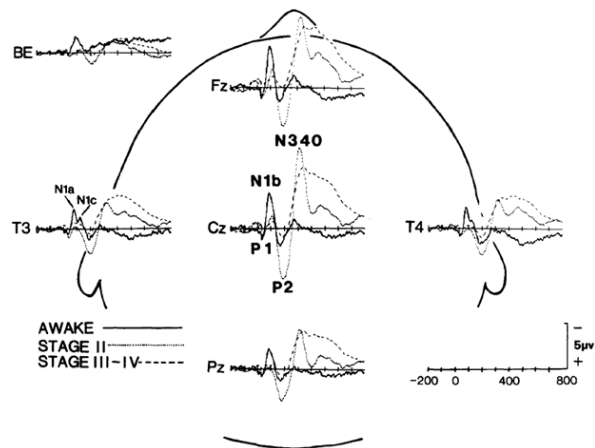
I.4.2. Brain responses to external stimulations

I.4.2.1. Sensory stimulations

In sleep, thresholds of perceptions increase (Rechtschaffen et al. 1966). The first assumption advanced to explain the loss in sensory reactivity during sleep was the thalamic gating hypothesis (Steriade et al. 1993b; McCormick and Bal 1994). The switch from tonic to phasic burst firing mode of the thalamus, associated with the hypersynchronisation of the thalamo-cortical network, may prevent the integration of external stimuli. However, the loss of sensory integration may finally be better explained by both thalamic and cortico-cortical levels, still enabling possible reactions of the sleeping brain to external stimuli.

Indeed, electrophysiological and imaging methods have since demonstrated clear activations to external stimuli in sensory cortices, suggesting that first stages of sensory processing are, at least, partially preserved. In animal studies, activations of auditory cortices in response to auditory stimuli during NREM and REM sleep have been directly recorded in single cells in pigs (Peña et al. 1999; Edeline et al. 2001), rats (Nir et al. 2013), primates (Issa and Wang 2008). In humans, fMRI activations to sounds were found in the thalamus and auditory cortices (Portas et al. 2000; Czisch 2002a; Wehrle et al. 2007; Dang-Vu et al. 2011). In scalp EEG and MEG, despite a short delay (Bastuji et al. 1995; Nordby et al. 1996), amplitudes of the first cortical evoked potential (P1, ~50 ms) were generally unchanged during sleep (Nielsen-Bohlman et al. 1991; Kitamura et al. 1996; Kisley et al. 2001). However, those cortical activations were sometimes found decreased or modified compared to wakefulness (Peña et al. 1999; Edeline et al. 2001; Czisch 2002a; Tanaka et al. 2003; Issa and Wang 2011; Issa and Wang 2008). Crucially, it has been shown that the transmission of sensory information to the cortex is strongly modulated by the specific sleep rhythms.

During sleep spindles, electrophysiological studies in animals demonstrated a strong decreased cortical reactivity to stimuli (Timofeev et al. 1996). In humans, the few scalp EEG studies revealed contrasting results (Elton et al. 1997; Cote et al. 2000), but in a more recent fMRI study, Dang-vu et al. (2011) showed that auditory presented stimuli in the presence of sleep spindles did not activate either the thalamus or auditory cortices, while they did in their absence. Highly synchronized thalamo-cortical rhythms during sleep spindles may then indeed operate a strong sensory gating, in line with earlier hypothesis (Steriade 1991; Steriade 2003).



Nielsen-Bohlman et al. (1991)

Figure 15. Auditory evoked potentials during wakefulness and NREM sleep

In sleep, amplitudes of the first evoked potentials are preserved (P1). In NREM sleep, auditory stimuli frequently elicit large K-complexes, leading to significantly increase amplitudes of later potentials.

However, K-complexes and slow waves appear to still enable sensory information to reach the cortex. From recent animal studies, it has been suggested that the burst firing mode of the thalamus during sleep may be as efficient to transfer information to the cortex as its tonic firing mode during wakefulness (Sherman 2001). Noteworthy, even during the DOWN phase of slow oscillations, sensory information may be transferred to the cortex (Massimini et al. 2003; Rosanova and Timofeev 2005), despite higher variability in latencies and amplitudes of cortical potentials.

In NREM sleep, sensory stimulations also frequently elicit large K-complexes (Bastuji and García-Larrea 1999), leading to large amplitude evoked potentials (Nielsen-Bohlman et al. 1991; Bastuji et al. 1995). The significance of those evoked K-complexes compared to the spontaneous ones remains debated, some considering it as an arousal phenomenon and others as a sleep-promoting response to a potentially arousing stimulus (Colrain 2005). Nevertheless, the physiological origin of evoked K-complexes is very similar to slow waves (and to spontaneous K-complexes), both emerging in the cortex from synchronous thalamo-cortical oscillations (Amzica and Steriade 2002) with frontal predominance (Cote et al. 1999; Wennberg 2010). In humans, evoked K-complexes to auditory stimuli are associated with larger fMRI responses in bilateral primary auditory cortices with spread activations in ventral and medial prefrontal cortices similar to activations during slow waves (Czisch et al. 2009; Dang-Vu et al. 2011). Those late KC activations have also been shown to be largely sensory modality independent (Riedner et al. 2011). Evoked K-complexes are then actually more largely considered as a sleep-specific pattern similar to slow waves (Wauquier et al. 1995; De Gennaro et al. 2000; Amzica and Steriade 2002) and interpreted as a stereotypical response of the thalamo-cortical system (Amzica and Steriade 2002).

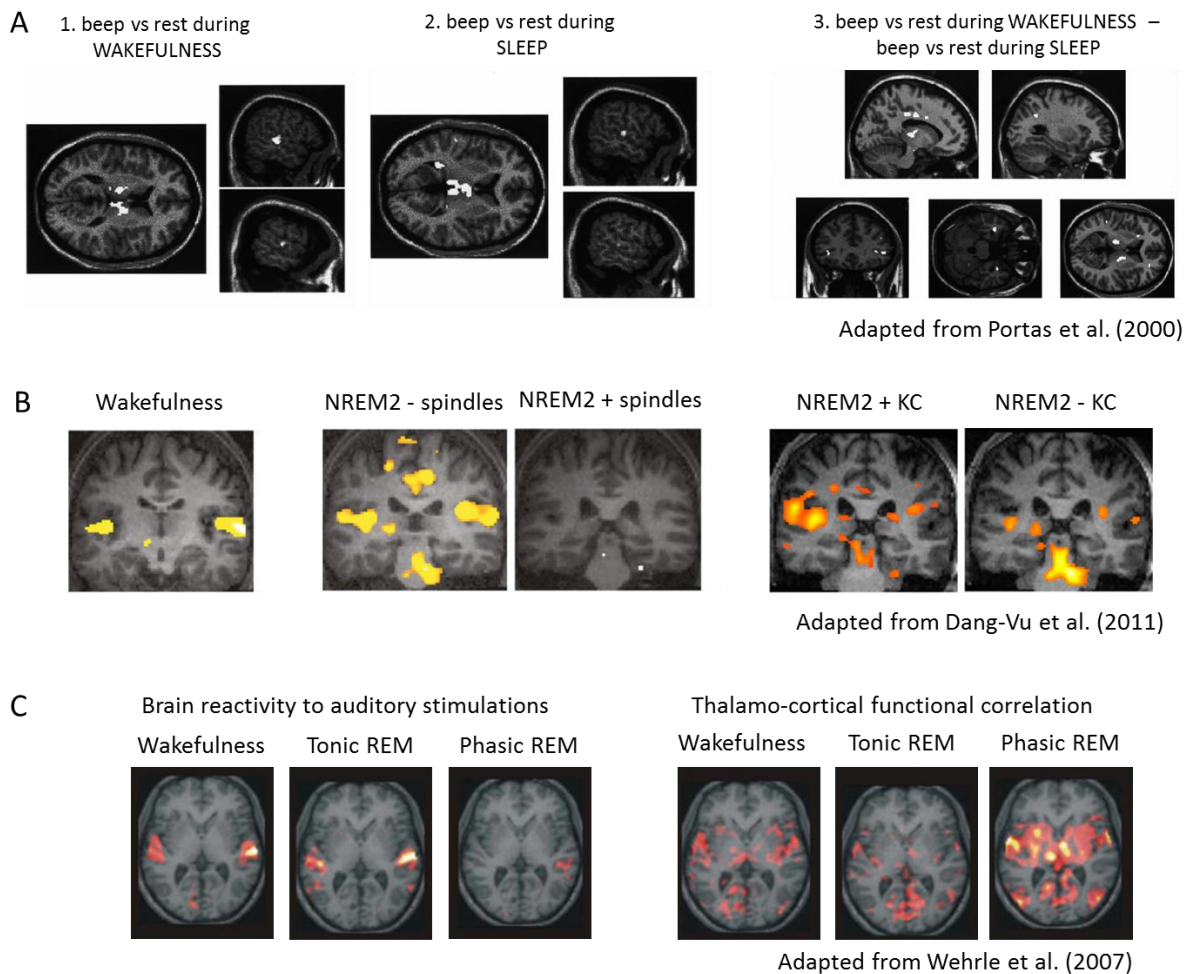


Figure 16. fMRI activations elicited by auditory stimulations and interaction with endogenous activities

A. 1 and 2: Auditory stimuli elicit bilateral activations of auditory cortices, thalamus and caudate similarly during wakefulness and NREM sleep. 3: Prefrontal, cingulate and left parietal cortices are nevertheless less activated in NREM sleep than in wakefulness.

B. Activations in auditory cortices are preserved during sleep in response to auditory stimuli, except during sleep spindles, during which activities are less consistent. When a K-complex is elicited, activations are enhanced in auditory areas and spread to frontal, similarly to stereotypical pattern associated with slow waves.

C. Brain reactivity to auditory stimuli and thalamo-cortical correlation in wakefulness, tonic REM and phasic REM sleep. Sensory cortices activations are significantly decreased in response to auditory stimulations in phasic REM compared to wakefulness and tonic REM sleep. Thalamo-cortical network including limbic and para-hippocampal areas much strongly active during phasic REM sleep than in the two other conditions.

Yet, evoked K-complexes still reveal some information processing, as they are larger in amplitude, especially the N550 component, when they are elicited by rare deviant sounds (Bastuji et al. 1995; Colrain et al. 2000). Also, they are elicited less frequently and with decreased amplitude with the repetition of the stimuli (Ujzászi and Halász 1988; Caekebeke et al. 1990), thus appearing to reflect habituation processes to external sensory stimuli. Habituation, or sensory adaptation, which has been shown to take place in primary cortices (Ulanovsky et al. 2003; Farley et al. 2010; Fishman and Steinschneider 2012), would be then preserved during sleep, as also suggested by recent an electrophysiological study in rats (Nir et al. 2013). As we shall see, our own results concord with this conclusion (Strauss et al. 2015).

In REM sleep too, sensory integration seems to be modulated by variations in endogenous activities. Information integration of external stimuli has been shown to be increased in tonic REM sleep (between REMs periods) compared to phasic periods (during REMs periods). For example, deviant tones elicit larger responses in ERPs during tonic REM sleep (Sallinen et al. 1996; Takahara et al. 2002). Interestingly, one study showed that those deviant-related potentials were even larger in tonic REM when subjects were asked, before sleep, to pay attention to the stimuli during their sleep (Takahara et al. 2006a), suggesting possible attentional mechanisms to external stimuli in tonic REM sleep, but not in phasic REM sleep. In fMRI also, auditory cortices have been shown to be much more reactive to auditory stimulations during tonic REM sleep (Wehrle et al. 2007). The decreased integration of external information during phasic REM sleep may be explained by the stronger thalamo-cortical activations and synchronization that occur during phasic REM sleep compared to tonic REM sleep (Steriade et al. 1989; Wehrle et al. 2007), that would thus isolate the brain from environmental stimulations; an hypothesis first advanced by Llinas and Paré (1991), who described the brain during REM sleep as a closed thalamo-cortical loop of sustained intrinsic neuronal activity.

To summarize, sensory information is not integrated in the same way within cortical areas depending on the ongoing background of sleep oscillations. NREM sleep spindles and phasic REM sleep, in strongly recruiting thalamo-cortical networks, seem to operate efficient sensory gating. Thalamo-cortical interactions appear then critical for sensory integration. However, for most of the time, external stimuli do reach sensory cortices. We will now see whether the information contained in stimuli is then further integrated within the cortical hierarchy, through associative areas and cognitive domains.

1.4.2.2. Reaction to the subject's own name

Reaction of sleeping subjects to their own name is particularly suited to study information integration during sleep as the stimulus is personally related, has an affective significance and can be relevant for waking-up. Indeed, we have known for a long time that the arousal threshold is lower for personally significant stimuli (Langford et al. 1974).

ERPs and fMRI studies confirm the deeper processing of subject's own name during sleep. When subjects are presented with their own name, ERPs differ from those elicited after other names in both NREM and REM sleep (Perrin et al. 1999). During NREM sleep, when the subject's own name does not wake up the subject, it tends to elicit more K-complexes (Oswald et al. 1960), which differ from other name responses by a positive effect around 600ms (Perrin et al. 1999). In REM sleep, a significant positive effect is also detected around 550 ms.

In fMRI during NREM sleep, own names compared to tone leads to increased activations in auditory cortices and specific activations in left amygdala and left prefrontal cortex (Portas et al. 2000), well in line with the affective valence and deeper processing of own names. This last study also shows that limbic structures can be significantly activated by external stimuli.

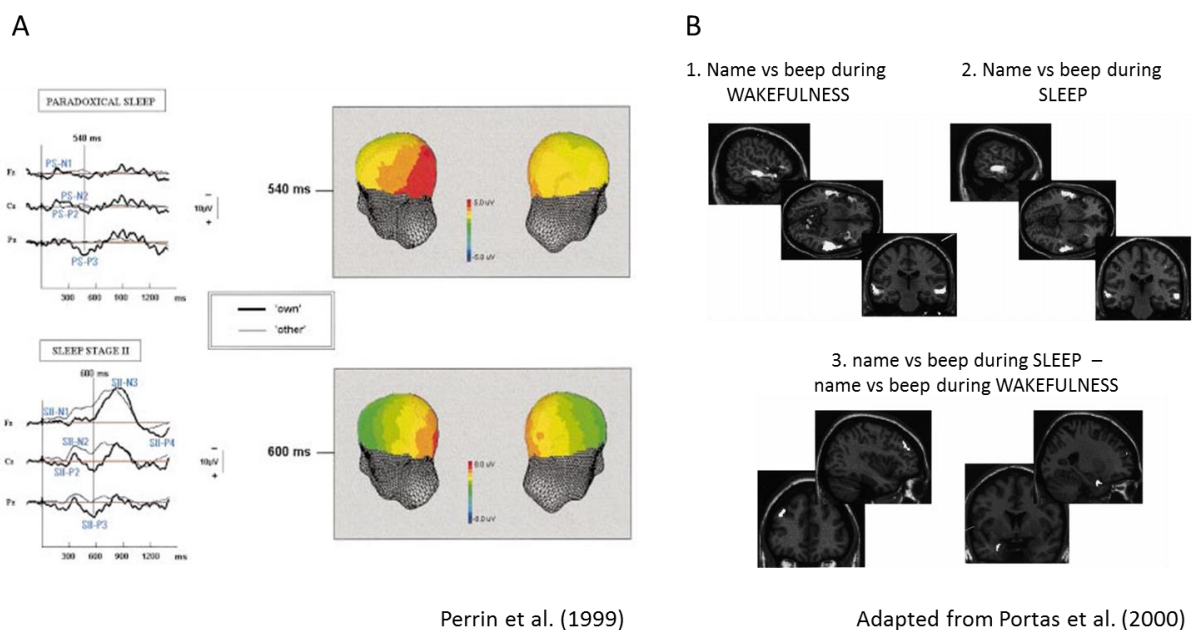


Figure 17. Reaction to subject's own name

A. Event related potentials to own name versus other names. Own names elicit late positivities (P540 in REM sleep and P600 in NREM2 sleep) in comparison to other names

B. 1 and 2: fMRI activations to own name vs beep. Middle temporal gyri and the orbitofrontal cortex are more activated in both wakefulness and sleep in response to name compared to beep. 3: During sleep, names also elicit a higher activation in the left amygdala and left prefrontal cortex

1.4.2.3. Semantic integration

Some studies have attempted to study semantic integration during sleep and reported uncourageous results. As we saw earlier, in ERPs during wakefulness, semantic integration is assessed by the presence of a negative wave elicited around 400 ms after semantic incongruity, the so-called N400 (Kutas and Hillyard 1980). The N400 has a centro-parietal topography and its amplitude is strongly correlated with the level of incongruity relative to the context (Kutas and Federmeier 2000).

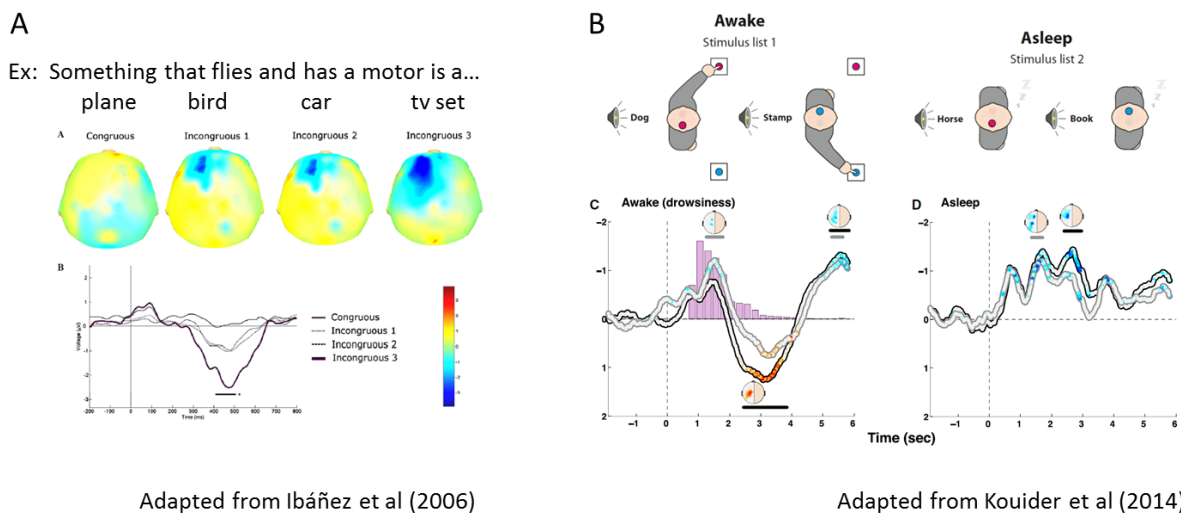


Figure 18. Semantic integration during sleep.

A. A late negative wave, supposedly an N400, is elicited by incongruent words during sleep in both NREM and REM sleep (here data from REM sleep). Its amplitude increases with the degree of incongruence.

B. Subjects continue to show signs of motor preparation (lateralized readiness potentials) during sleep in response to presented words, after they had previously performed during wakefulness a motor task of semantic categorization.

All published studies reported a negative deflection similar to the N400 in both NREM2 and REM sleep after incongruous words compared to congruous ones (Brualla et al. 1998; Perrin et al. 2002; Ibáñez et al. 2006; Daltrozzo et al. 2012). In order to assess lexical and semantic discordance hierarchy, Perrin et al. (2002) used pseudo-words in addition to congruent and incongruent words, and found that the hierarchy congruent/pseudo-word/incongruent was lost during NREM sleep and modified in REM sleep, with then a similar process for both pseudo-words and congruent ones. They suggested that this may have been the consequence of the 'hyper associative' state of REM sleep, which would lead to consider absurd content as plausible. In the same line, Ibanez et al. (2006) tested semantic processing hierarchy using different levels of word congruency relative to the context: congruent, partially incongruent, and totally incongruent words. Although the topography was quite

anterior (but in sleep as in wakefulness), they showed a N400-like in both NREM and REM sleep, which was significantly modulated in amplitude by the level of congruency (the most incongruent elicited the highest N400-like). In the Daltrozzo et al. (2012) study, authors also claimed to have found a N400-like effect during NREM2 and REM sleep, however their ERPs were quite noisy and even the auditory evoked potential was barely seen.

Finally, Kouider et al. (2014) also suggested semantic integration in NREM1 and NREM2 sleep in recording signs of motor preparation in response to a semantic-related task. Subjects were presented during wakefulness with either animal or object names and were asked to give a lateralized motor respond depending of the semantic category (left or right hand). Interestingly, once asleep, subjects still exhibited adapted lateralized-readiness-potential in EEG recordings when presented with words of one or the other semantic category. Similar results were obtained with a lexical decision task (word versus pseudo-word). This study then demonstrated that during early sleep, subjects still process semantic information, but are also able to generate task-relevant motor preparation.

1.4.2.4. Cueing to enhance memory consolidation during sleep

An important advance in sleep research which has been done recently is the discovery that we can influence memory consolidation during sleep through external stimulations. In presenting fragments or cues of previous learning during sleep, associated memories are preferentially replayed and consolidated in long term memories.

The first experiments were done in the 1980's on rats during REM sleep by Hennevin and collaborators. Using avoidance conditioning, they showed that presenting the conditioned stimulus during REM sleep improved post sleep performances (Hars et al. 1985) and elicited during sleep increased hippocampal discharges (Maho et al. 1991). They also showed that electrical stimulation of the mesencephalic reticular formation during post-learning REM sleep could improve performances (Hennevin et al. 1989). The memory consolidation benefits of cueing in humans was then first investigated in presenting Morse codes previously learned during wakefulness in REM sleep (Guerrien et al. 1989), or clicks that were also presented during the learning phase (Smith and Weeden 1990). Noteworthy, those first studies showed significant improvement in performances only when stimuli were presented during the REMs periods. This contrasts with data on sensory processing, which showed less integration through cortical areas during phasic REM sleep. However, REMs have been associated with PGO waves, which enhance plasticity and memory consolidation. If they are relevant and activate information stored in memory, stimuli may then be further integrated and promote memory consolidation. Based on those previous results, one more recent study used auditory cues during phasic REM sleep in a visual recognition task (Sterpenich et al. 2014), and confirmed the benefit of cues on memory consolidation. Moreover, interestingly, cues enhanced memory performances but also false

recognitions. This was interpreted as a consequence of the extraction of generic features about pictures during REM sleep, leading to large semantic associations and the subsequent confusion between seen and non-seen pictures.

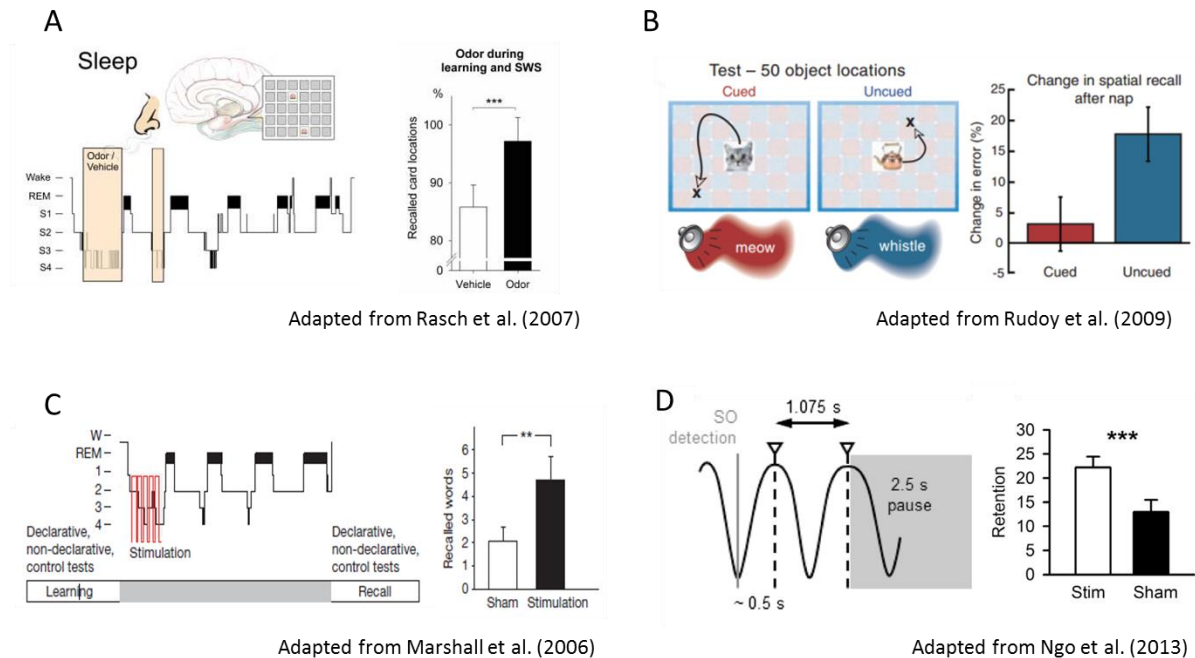


Figure 19. Enhancing memory consolidation with external stimulations

A and B. Cueing during sleep. Subjects first learn a visuo-spatial memory task, while odors (A) or sounds (B) are presented in association to stimuli. Presenting again the odors or sounds during the subsequent sleep improves memory performances.

C and D. Boosting slow oscillations. Transcranial current stimulation at 0.75 Hz (C) or tones presented in phase with the UP state of slow oscillations (D) increase delta power and memory consolidation.

Recent studies also demonstrated the benefit of cueing during SWS. Rasch et al. (2007) presented odors – capitalizing on their powerful faculty to cue contextual memories retrieval –, during learning of a visuo-spatial memory task and during subsequent sleep. Retrieval performances were significantly improved when the odor was presented during SWS in comparison to control conditions (vehicle during SWS, odor/vehicle during REM sleep, odor/vehicle during waking). The odor presentation was associated with reactivations in the hippocampus during SWS, as shown by fMRI acquisitions, and with increased delta power and sleep spindle as shown in a later study (Rihm et al. 2014). Rudoy et al. (2009) presented sounds associated with items in a similar visuo-spatial task, which were also presented during the subsequent SWS. Again, items cued during sleep were better remembered than others not cued, and were associated in a later study with increased activation in the right parahippocampal cortex (van Dongen et al. 2012). Antony et al. (2012) also showed that a tone sequence played in ‘piano’ could be better remembered when the melody was played during post

learning SWS, with performances positively correlated with the density in slow waves and sleep spindles. All these studies suggest that different types of cueing can trigger hippocampal replay and associated slow waves and spindles, and eventually improve memory consolidation. This was confirmed in rats with direct recordings of the reactivation of hippocampal cells involved in learning following auditory cues during SWS (Bendor and Wilson 2012). Interestingly, cues during SWS have been shown to stabilize memories and increase resistance to interference, in contrast to cueing during wakefulness that destabilized memories (Diekelmann et al. 2011).

Presenting fragments of previous learning during sleep is not the only way to improve memory consolidation. Marshall et al. (2006) managed to enhance slow waves by repetitive transcranial stimulation at low frequencies (0.75Hz), which lead to improve retention of hippocampus-dependent declarative memories. The same group then showed that slow waves could also be enhanced by auditory stimulation delivered in phase to UP states of slow waves (Ngo et al. 2013; Ngo et al. 2015), leading similarly to memory improvement.

1.4.2.5. Learning during sleep

If strong evidence supports the role of sleep in consolidation of previously learnt memories, it is much less evident that we can *learn* new information during sleep. Intuitively, sleep is a moment of rest with a minimum of external stimulations and therefore should not be the best moment for learning new material. However, a number of researchers attempted for a long time to look for sign of learning during sleep, probably attracted by the idea that we could learn without any effort. Unfortunately, their research was largely unsuccessful (Emmons and Simon 1956; Simon and Emmons 1956; Bruce et al. 1970; Lehmann and Koukkou 1974; Wood et al. 1992).

It is only recently that Arzi et al. (2012) succeeded in demonstrating some learning during sleep. Using partial-reinforcement trace conditioning, they presented pleasant and unpleasant odors associated with paired-tones or tones alone during sleep. Odors elicit an automatic sniff whose the volume is larger for pleasant odors, what they found during sleep. During post sleep wakefulness, they then presented tones alone, and found that tones previously associated with pleasant odors elicited a larger sniff volume that tones presented with unpleasant odors. Noteworthy, this effect of conditioning took place already during sleep in NREM and in REM sleep, but during wakefulness only tones presented during NREM sleep lead to larger sniff volume. Thus, they managed to demonstrate that a simple form of implicit learning as conditioning can still be performed during sleep.

Even more recently, in mice this time, Lavilleon et al. demonstrated that they could create new goal-directed behavior during sleep (de Lavilléon et al. 2015). They created artificial place-reward associations in stimulating the medial forebrain bundle in the same time than the spontaneous activity

of a given place cell during sleep. After sleep, mice moved directly toward the corresponding place field. Author suggested then that they could create *explicit* memory trace leading to goal-directed behavior.

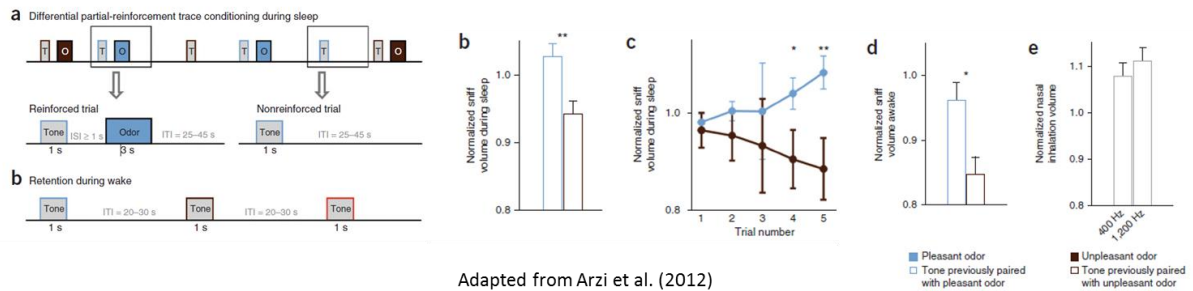


Figure 20. Learning during sleep

Tones were presented during sleep followed by pleasant or unpleasant odors, or alone. During sleep, tones alone that were previously associated with pleasant odors triggered a sniff reaction with a higher volume than tones previously associated with unpleasant odors. During wakefulness post sleep, tones that were previously associated with pleasant odors continue to trigger a higher sniff response.

1.4.2.6. Novelty detection and search for potential signatures of consciousness during sleep

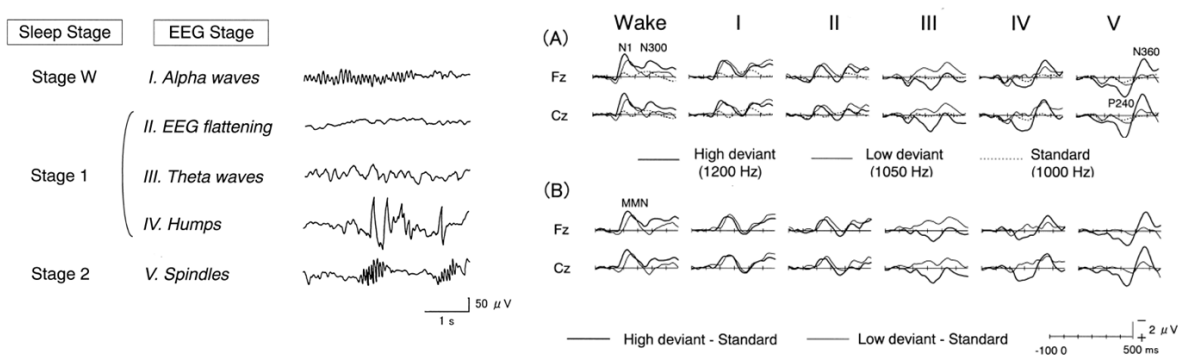
The ability to detect changes in the environment is crucial for survival. Sleep, with its recurrent loss of awareness of the environment, appears as a condition of extreme vulnerability. Whether the human sleeping brain continues to detect changes or novelty, to eventually wake up, is then a crucial question. This question was indeed assessed for a long time but, surprisingly, no clear conclusion has been reached.

For at least 30 years, successive studies have attempted to record ERPs correlates of auditory novelty in recording brain responses to rare deviant sounds presented within series of standard ones, the so-called oddball paradigm. As previously described, two main novelty-related ERPs are elicited: the mismatch negativity (MMN), a fronto-central negative component peaking at around 150 ms after deviant tones (Näätänen et al. 1978) and believed to reflect pre-attentive automatic processes (Näätänen et al. 2001), and the P300 or P3b, the late and sustained positivity recorded in posterior areas (Sutton et al. 1965) and putatively associated with conscious access (Dehaene and Changeux 2011).

Both of them have then been actively researched during sleep, assessing novelty detection capabilities of the sleeping brain, but in the same way potential conscious processing through the P300.

I.4.2.6.1. MMN

Despite the somewhat robust appearance of the oddball paradigm, results were highly divergent in almost all sleep stages. In NREM1, studies were quite balanced between positive (Winter et al. 1995; Nashida et al. 2000; Sabri et al. 2003; Ruby et al. 2008a) and negative results (Paavilainen et al. 1987; Sabri et al. 2000; Yang and Wu 2007). This mixed results may be explained by the various ‘micro-stages’ that compose NREM1 sleep as defined by Rechtschaffen and Kales (1968). Hori et al. (1994) provided a much more precise definition of the descent to sleep, based on 5 s-epochs, comprising a succession of 9 distinct rhythms from alpha waves to sleep spindles. Based on 5 of these micro-stages, *i*) alpha waves (wakefulness), *ii*) EEG flattening, *iii*) theta waves, *iv*) humps (vertex sharp wave burst), and *v*) spindle (NREM2), Nittono et al. (2001) assessed the evolution of the MMN when falling asleep. They nicely demonstrated the gradual decrease of the MMN and its vanishing from the emergence of theta waves (stage *iii*). From this point, high deviant tones (1200 vs 1000 Hz) still elicited a significant effect, but made of a succession of P240 and N360 waves. Noteworthy, deviants close in frequency to the standard (1050 vs 1000 Hz) did not elicit any significant effect.



Adapted from Nittono et al 2001

Figure 21. Gradual decrease and vanishing point of the MMN during NREM1 sleep

NREM1 sleep is subdivided in 3 Hori stages. In the descent to sleep, the MMN amplitude gradually decreases to vanish from the appearance of theta waves. (A) High deviant, Low deviant and standard tones. (B) Differences deviant – standard tones (MMN).

Three conclusions can be drawn from this study: *i*) the classical 30s-epoch NREM1 sleep stage, albeit still useful in clinics, is very poor in defining the precise cognitive steps in the transition to sleep, *ii*) the MMN seems to remain despite the EEG flattening, but vanish once theta waves occur, and *iii*) a mismatch effect, different from the MMN (P240-N360), persist in NREM2 for high deviant tones only.

In accordance with this conclusion, the majority of studies failed to record the MMN in NREM2 (Paavilainen et al. 1987; Nielsen-Bohlman et al. 1991; Nordby et al. 1996; Loewy et al. 1996; Winter et al. 1995; Sallinen et al. 1997; Loewy et al. 2000; Nashida et al. 2000; Yang and Wu 2007) and most of them instead reported a later significant positive effect (~220ms), sometimes followed by a late negativity (~350 ms) which tended to be related to the presence of K-complexes (Nielsen-Bohlman et al. 1991; Sallinen et al. 1994; Winter et al. 1995; Sallinen et al. 1997; Yang and Wu 2007).

In REM sleep also, the two studies which did not find the MMN reported in one case a P210 (Sallinen et al. 1996), and in the other a negativity between 300 and 400 ms (Loewy et al. 2000). Interestingly, the P210 reported by Sallinen et al. was larger in tonic REM than in phasic REM sleep, reinforcing the idea that the brain is less responsive to the environment during periods with REMs than in between.

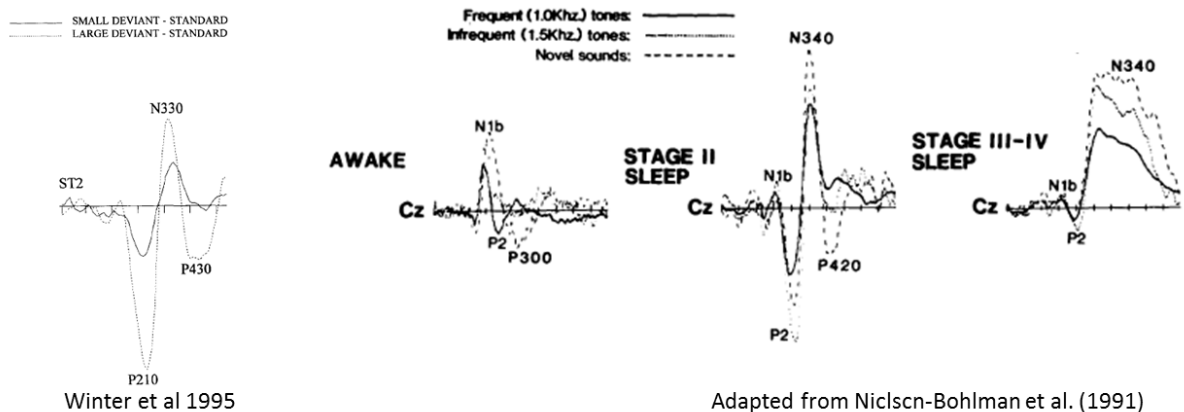


Figure 22. Examples of MMN not found during sleep

Left. MMN to large (2000 Hz) and small (1200 Hz) deviants in NREM2 sleep (standards 1000 Hz).
 Right. ERPs elicited after deviant (1500 Hz) and standard (1000 Hz) tones in wakefulness, NREM2 and SWS.

However, a non-negligible number of studies did report a MMN-candidate or ‘deviant-related-negativity’ during sleep, mostly in REM sleep. Among the positive results, most of them used large intensity deviants (2000 Hz vs 1000 Hz; in NREM (Sabri et al. 2000; Sabri et al. 2003; Sabri and Campbell 2005; Ruby et al. 2008a) and REM sleep (Atienza et al. 1997; Nashida et al. 2000; Sabri and Campbell 2005; Ruby et al. 2008a)). This MMN-candidate was yet very often decreased in amplitude (Loewy et al. 1996; Atienza et al. 1997; Nashida et al. 2000; Ruby et al. 2008a; Sabri et al. 2003) and, surprisingly, had shorter latencies than during wakefulness (Loewy et al. 1996; Nashida et al. 2000; Atienza and Cantero 2001; Ruby et al. 2008a; Sabri et al. 2003; Sabri and Campbell 2005). Interestingly, Sculthorpe et al. (2009) were the rare authors to use a different paradigm to assess auditory novelty detection during sleep. They measured brain responses to deviant sound *repetitions* in an alternating ABAB paradigm. They were able to detect a MMN-candidate during REM sleep, but for large deviants only (6 semitones compared to 1 semitone), and no effect was observed during NREM sleep.

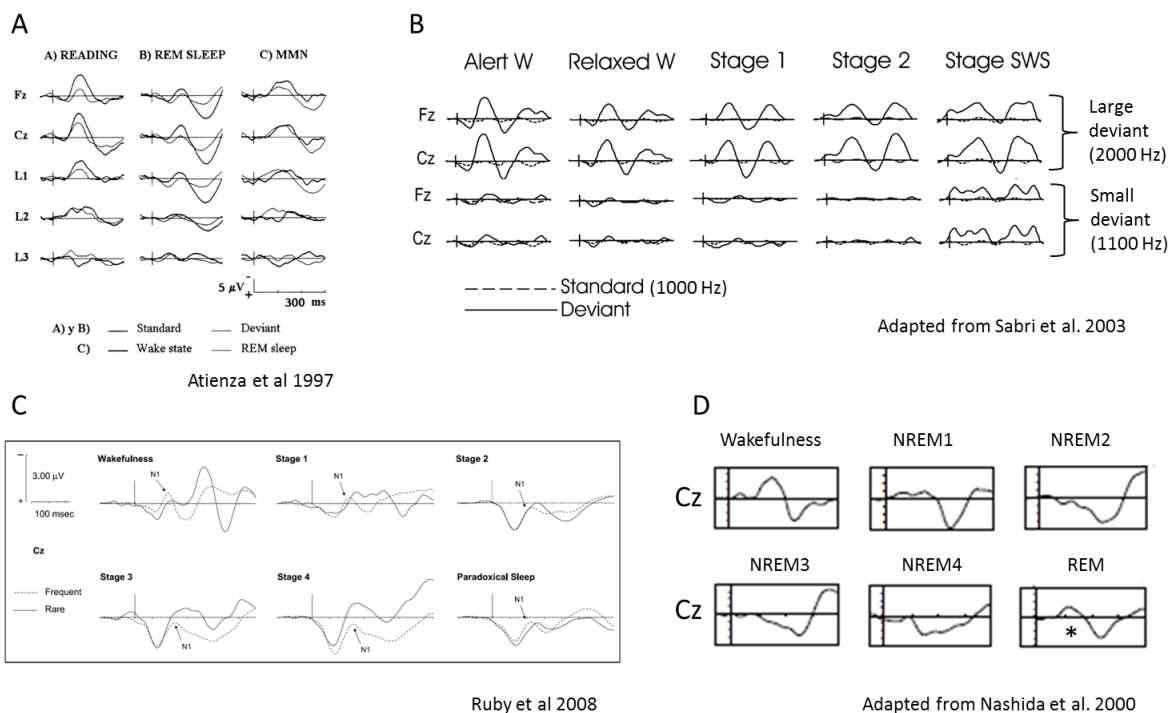


Figure 23. Examples of MMN found during sleep.

A. MMN found in REM sleep. B. MMN found in NREM1, NREM2 and SWS. C. MMN found in all sleep stages. D. MMN only found in REM sleep.

Mismatch Negativity (MMN) - candidate						
	FOUND			NOT FOUND		
	Study	Comments	N	Study	Comments	N
NREM1	Winter et al. (1995) Nashida et al. (2000) Sabri et al. (2003) Ruby et al. (2008) Nittono et al. (2001)	* Contains waking periods * Automatic analysis of sleep stages on EEG frequencies only – Shorter latency than during wakefulness * Large deviant only * N154 – P274 * Early N1	5	Paavilainen et al. (1987) Sabri et al. (2000) Nittono et al. (2001) Yang et Wu. (2007)	- - * Late N1, P240 – N360 * N350	4
NREM2	Sallinen et al. (1994) Sabri et al. (2000) Sabri et al. (2003) Sabri et Campbell (2005) Ruby et al. (2008)	* Only with KC, failed to reproduce this result later * Large deviant only, not found in NREM1 in the same study * Large deviant only, decreased amplitude and shorter latency * Large deviant only, shorter latency * Large deviant, decreased amplitude and shorter latency; P249	5	Paavilainen et al. (1987) Nielsen-Bohlman et al. (1991) Winter et al. (1995) Nordby et al. (1996) Loewy et al. (1996) Sallinen et al. (1997) Loewy et al. (2000) Nittono et al. (2001) Nashida et al. (2000) Yang et Wu. (2007)	- * P2 (130-255 ms) – N340 * P210 – N330 - - * P210; with KC; P210 – N350 * N300-400 * P240 – N360 * Automatic analysis of sleep stages on EEG frequencies only * P220 – N350 – P900	10
SWS	Sabri et Campbell (2005) Ruby et al. (2008)	* Large deviant only * Large deviant, negative drift	2	Nielsen-Bohlman et al. (1991) Loewy et al. (1996) Sabri et al. (2000) Nashida et al. (2000) Yang et Wu. (2007)	* Non-significant N340 * N350 - * Automatic analysis of sleep stages on EEG frequencies only * P220 – N350 – P900	5
REM	Loewy et al. (1996) Atienza et. al (1997) Nashida et al. (2000) Atienza et Cantero (2001) Sabri et Campbell (2005) Ruby et al. (2008) Sculthorpe et al. (2009)	* Shorter latency for small deviants, decreased amplitude for large deviants * Large deviant, decreased amplitude * Automatic analysis of sleep stages on EEG frequencies only – large deviant, decreased amplitude and shorter latency * Shorter latency * Large deviant only, shorter latency * Large deviant, decreased amplitude and shorter latency; P263 * Large deviant only	7	Sallinen et al. (1996) Loewy et al. (2000)	* P210, larger in tonic than in phasic REM sleep * N300-400	2

Figure 24. MMN: Review of oddball studies during sleep

Studies which claimed to have found a MMN or not in the different states of vigilance are listed. Comments and latencies of the effects found are reported.

I.4.2.6.2. P300

In the transition to sleep, the P300 has been found with decreased amplitude (Bastuji et al. 1995). Studies that analyzed precise changes in EEG rhythms or behavior in the descent to sleep found a P300 with a slightly delayed latency before the occurrence of theta rhythms (Niiyama et al. 1994; Winter et al. 1995) or when subjects were still responsive (Harsh et al. 1994; Hull and Harsh 2001), but not later in NREM1. Here again, these studies reveal that NREM1 is a heterogeneous stage that embeds different levels of cognitive capabilities in the transition to sleep.

P300 - candidate						
REPORTED AS FOUND			REPORTED AS NOT FOUND			
	Study	Comments	N	Study	Comments	N
NREM1	Harsh et al. (1994) Niyama et al. (1994) Winter et al. (1995) Ruby et al. (2008)	* responsive subjects, longer latency P405 * early NREM1, P405 * drowsiness with alpha rhythms; P430 * P250 – not present in wakefulness	4	Harsh et al. (1994) Niyama et al. (1994) Hull and Harsh (2001)	* not responsive subjects; P220 – N350 – P450 * late NREM1 (theta rhythms) -	3
NREM2	Nielsen-Bohlman et al. (1991) Ruby et al. (2008)	* P2 (130-255 ms) – N340 – P420 * P250 – not present in wakefulness	2	Paavilainen et al. (1987) Wesensten and Badia (1988) Niyama et al. (1994) Harsh et al. (1994) Winter et al. (1995) Bastuji et al. (1995) Nordby et al. (1996) Cote and Campbell (1999a) Cote and Campbell (1999b) Cote et al. (2001) Hull and Harsh (2001) Takahara et al. (2006) Yang et Wu (2007)	- Possible P200 - * P220 – N350 – P450 – P900 * P210 – N330 – P430 * P450 - * P450; P450 – N550 when KC+ * P200 – N330 – N550 (KC+) * P250 * P220 – N350 – P450 – N550 – P900 * P200 – P450 – N550 * P220 – N350 – P900	13
SWS	Wesensten and Badia (1988)	* N400 – P700	1	Nielsen-Bohlman et al. (1991) Niyama et al. (1994) Ruby et al. (2008)	* P2 (130-255 ms) – N340 * N412-P868 * N150	3
REM	Wesensten and Badia (1988) Niyama et al. (1994) Bastuji et al. (1995) Sallinen et al. (1996) Cote and Campbell (1999a) Cote and Campbell (1999b) Cote et al. (2001) Ruby et al. (2008)	* P700 * P361 * P455 * P210 – P450-550 * P321 – only loud (90dB) intensity deviant * P363 – only loud (100dB) intensity deviant * P300-500 – only very rare (5%) intensity (vs pitch) deviant (100 dB) * P250 – not present in wakefulness	8	Nordby et al. (1996) Takahara et al. (2002) Takahara et al. (2006)	* late negativity * P200 – P400 * P200 – P400	3

Figure 25. P300: Review of oddball studies during sleep

Studies which claimed to have found a P300 or not in the different states of vigilance are listed. Latencies of the effects found are reported in the 'comments' column.

Most of the studies which claimed to found a P300 during sleep reported it during REM sleep (Wesensten and Badia 1988; Niyama et al. 1994; Bastuji et al. 1995; Sallinen et al. 1996; Cote and Campbell 1999a; Cote and Campbell 1999b; Cote et al. 2001; Ruby et al. 2008a), in contrast to NREM2 (Nielsen-Bohlman et al. 1991; Ruby et al. 2008a) and SWS (Wesensten and Badia 1988). Authors have then frequently interpreted this P300 as a correlate of consciousness during sleep, especially as it was mostly found in REM sleep. However, the positivity interpreted as a P300 was often quite late compared to wakefulness, around 450 ms (Bastuji et al. 1995; Sallinen et al. 1996; Nielsen-Bohlman et al. 1991) or even later at 700 ms (Wesensten and Badia 1988). Besides, those who found a P300-candidate around 350 ms in REM sleep did so with very loud intensity deviants (Cote and Campbell 1999a; Cote and Campbell 1999b; Cote et al. 2001) at 90 or 100 dB (which is equivalent to the sounds of a klaxon or a jackhammer at 2 meters...), or failed otherwise (with lower dB or pitch deviants). These very loud deviant tones may have elicited micro-arousal, which were not mentioned as removed in these studies. We may suspect that potential awakening trials may have evoked stronger responses than those which did not elicit micro-arousals. Finally, Ruby et al (2008) interpreted a significant P250 in NREM2 and REM sleep as a P300, although they could not find it in wakefulness.

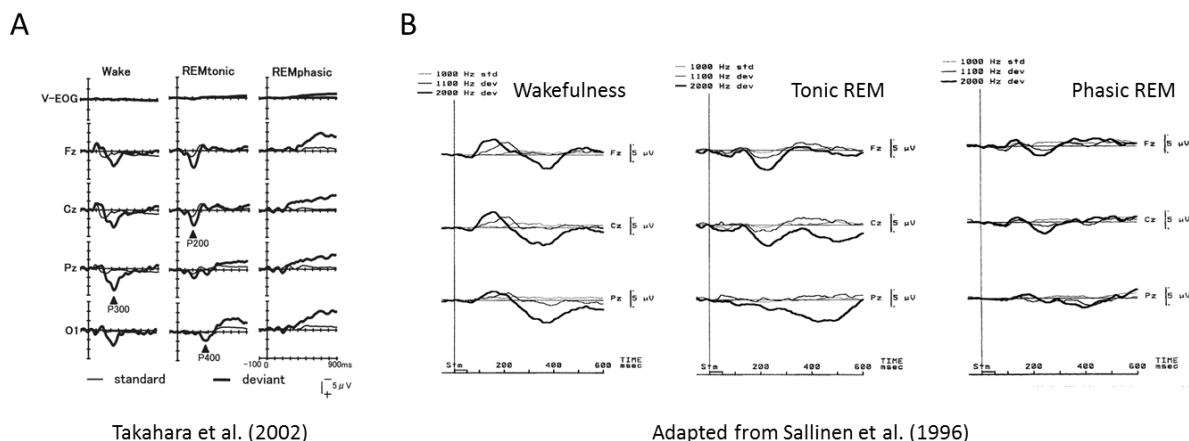


Figure 26. Event-related potentials to deviant versus standard sounds in tonic and in phasic REM sleep

In wakefulness, deviant tones elicit a centro-posterior P300. In both studies, deviant tones elicit a central positivity around 200 ms and a posterior positivity around 400 ms in tonic REM sleep, but no significant effect could be observed during phasic REM sleep. This suggests a higher processing of external stimuli in tonic REM sleep. Note that in (A) those potentials were labelled P200 and P400, while the later one was interpreted as a P300 in (B). Besides, no MMN was mentioned in those studies.

Among studies which did not report a P300, most of them were in NREM2 sleep (Paavilainen et al. 1987; Wesensten and Badia 1988; Harsh et al. 1994; Hull and Harsh 2001; Niiyama et al. 1994; Bastuji et al. 1995; Winter et al. 1995; Nordby et al. 1996; Cote and Campbell 1999a; Cote and Campbell 1999b; Cote et al. 2001; Takahara et al. 2006a; Yang and Wu 2007) and SWS (Nielsen-Bohlman et al. 1991; Niiyama et al. 1994; Ruby et al. 2008), in contrast to a few in REM sleep (Nordby et al. 1996; Takahara et al. 2002; Takahara et al. 2006). Instead, they very often described an increased P2 (200 – 250 ms) following deviant tones (Nielsen-Bohlman et al. 1991; Harsh et al. 1994; Hull and Harsh 2001; Takahara et al. 2002; Winter et al. 1995; Cote and Campbell 1999b; Cote et al. 2001; Takahara et al. 2006; Yang and Wu 2007), and a later positivity around 450ms, but which in those studies was not interpreted as a delayed P300. Very often, it was interpreted in NREM2 as a component of K-complexes (Bastuji et al. 1995; Winter et al. 1995; Cote and Campbell 1999a; Harsh et al. 1994; Hull and Harsh 2001; Takahara et al. 2006). This P450 was indeed frequently associated with other components of the K-complex, also increased by deviant tones, namely N350, N550 and P900. In REM sleep, in an original study, Takahara et al. (2006) suggested that the late positivity recorded (here called P400) would reflect auditory attention processing. They indeed showed that in tonic REM, the P400 was larger when subjects were asked before sleep to try to detect deviant sounds during their sleep and give a motor response. Also, few motor responses were emitted in both NREM

and REM sleep (in REM sleep mostly during tonic REM), without eliciting a proper micro-arousal, i.e. an increased in EEG rhythms during at least 3 s. However, we may ask whether those motor responses would have not been produced during very short (maybe local) awakening of less than 3s. Nevertheless, these results suggest that voluntary attention may improve information processing during REM sleep.

In summary, using the oddball paradigm, studies consistently reported a significant effect of deviance during NREM or REM sleep, especially as large deviant tones were used (in pitch or intensity). Novelty detection thus seems to occur during sleep. However, the hierarchical effects described (MMN, P300 or others) and their interpretation strongly varied between studies:

i) Although the same paradigm was used, depending on studies some authors choose to report only the MMN effect (Nashida et al. 2000; Atienza et al. 1997; Atienza and Cantero 2001) and others only the P300 effect (Wesensten and Badia 1988; Niyama et al. 1994; Takahara et al. 2006a), and this even among the same group (MMN: Loewy et al. 1996; Sabri et al. 2000; Sabri et al. 2003; Sabri and Campbell 2005 – or P300: Cote and Campbell 1999a; Cote and Campbell 1999b; Cote et al. 2001). This choice seems here quite arbitrary.

ii) A deviant related positivity around or later than 300ms was interpreted as the P300 by some authors (whatever its latency – sometimes until 700ms, or exact topography), whereas it was not considered as such by some others.

But most importantly, all those studies that used the classical oddball paradigm, with rare deviant tones presented within series of standard ones could not assess the proper P300 and MMN.

i) First, the effect observed could simply rely on the physical difference between the two stimuli, as in the majority of these studies the role for both tones (deviant or standard) was not counterbalanced (with a few exceptions: (Hull and Harsh 2001; Yang and Wu 2007) counterbalanced across subjects, and (Ruby et al. 2008a) used duration deviants).

ii) Second, the positivities interpreted as P300 may have been confounded with the P3a, the positivity that follows the MMN just before the P300, but that can be elicited automatically in non-conscious conditions (Squires et al. 1975b).

iii) Third, as we saw earlier in the introduction, this oddball paradigm does not enable to extract the cognitive mechanism at the origin of the effect observed, i.e. whether the novelty effect is related to sensory adaptation or predictive coding mechanisms.

I.5. CONCLUDING REMARKS ON CONSCIOUSNESS DURING SLEEP

As a conclusion for this chapter, we saw that both sleep stages share common features. At the behavioral level, both have *i)* a reduced responsiveness and external awareness, *ii)* a preserved internal awareness during dreams – which are yet much frequent in REM sleep –, that misses some features of the wakefulness consciousness as volition and metaconsciousness. At the physiological level, we observe a partial or complete shutdown of the ascendant activating system and the deactivation of prefrontal cortices.

Notable differences have also been described in term of spontaneous activations:

- In NREM sleep, high frequency bursts of activation are still present during UP states of slow waves and spindles, during which the hippocampal replay occurs. It is associated with activations in hippocampo-cortical networks, localized in space at the cortical level. UP states of slow waves are also associated with activations in the default mode network. We suggest that awareness in dreams may be linked to the replayed information, which may occur in case of sufficient distribution and sustained activations through cortical areas (either in long UP states during SWS or more frequently during NREM2).

- REM sleep is characterized by regained activations in parts of the thalamo-cortical and cortico-cortical networks, with increased synchrony in the gamma frequency range similar to wakefulness. Thalamo-cortical activations are particularly strong during REMs periods – believed to be associated with PGO waves originating in the pons. This regain in thalamo-cortical and cortico-cortical activity is then coherent with more the frequent dreams reported from REM sleep. Noteworthy, volition and metaconsciousness may be regained in lucid dreaming with the reactivation of the fronto-parietal network.

In reaction to external stimulations, sensory cortices are activated and information can propagate to associative areas. These elicited activations are yet strongly dependent on ongoing spontaneous activations of sleep. When the thalamo-cortical network is engaged in intense processing of internal information (as during sleep spindles and phasic REM), external stimuli are much less deeply processed. Beyond the activations of associative areas, strong evidence for the existence of potential signature of external awareness is missing. Activations seem quite localized, but we miss frequency and connectivity analyses in order to assess the amount of information sharing in response to stimuli. Still, late and sustained activities have been recorded during sleep in both NREM2 and REM sleep, with putative N400 and P300 effects. The presence of the P300 during sleep would index conscious processing, which will dramatically change our view on sleep as a non-conscious state, at least considering external stimuli. As we saw, yet, it still remains to be confirmed whether the late positivity recorded in previous studies truly corresponds to the P300. I will tackle this question in the

chapter II of this manuscript. The presence of the N400 would suggest the presence of late and sustained activities, which could also index consciousness. I will assess this question in the chapter III.

Importantly, there is no certitude for explaining the dissociation between internal awareness that may be preserved during sleep on the one hand, and the apparent loss of external awareness on the other hand. The partial or complete shutdown of the ascending activating system may not fully explain this dissociation, as sensory information still reach primary cortices during sleep. It has been suggested, especially in REM sleep, that the brain is engaged in closed thalamo-cortical loops that prevent external information from entering consciousness (Llinás and Paré 1991). In addition, we suggest that another or associated factor could be the lack of *attention* towards external stimuli, which has been suggested to be critical for conscious access (Dehaene et al. 1998a; Dehaene and Naccache 2001; Dehaene et al. 2006; Dehaene and Changeux 2011). Indeed, brain networks that preferentially support external awareness, as the dorso-lateral prefrontal cortex, are deactivated during sleep (Maquet et al. 1990; Maquet et al. 1997; Braun et al. 1997; Andersson et al. 1998; Kajimura et al. 1999; Kaufmann 2006; Maquet et al. 1996; Braun et al. 1997; Nofzinger et al. 1997), whereas those which are believed to support internal awareness (Vanhaudenhuyse et al. 2010) show persistent activities, as mesiofrontal cortices and associated region of the default mode network (Horovitz et al. 2008; Murphy et al. 2009; Larson-Prior et al. 2009; Tagliazucchi et al. 2013a). Finally, we do not completely exclude that it may happen that the sleeping brain be conscious of external stimuli, but in this case we suggest that they would be incorporated into dreams, as it has been shown to sometimes occur in previous experiments (Hoelscher et al. 1981; Burton et al. 1988).

I.6. INTRODUCTION TO PERSONAL CONTRIBUTIONS

I.6.1. General objectives

The sleeping brain is not inactive; it actively processes internally generated stimuli in order to serve specific functions as memory consolidation and synaptic restructuring. The profound changes in brain rhythms lead to strongly reduce responsiveness to the environment and modify conscious states in all its dimensions. Behavioral reports suggest that awareness of the surroundings is drastically reduced, while internal awareness during dream mentation may persist. Physiological brain activities suggest that the putative signatures of consciousness are massively disrupted during sleep, but that some of them can still persist, especially during the hippocampal replay in NREM sleep and during REMs/PGO waves in phasic REM sleep. Those intense activities seem to prevent external stimuli to be deeply processed in the brain. Otherwise, external stimuli still reach sensory cortices, and may be processed through different cognitive domains. Again, despite much sparser evidence, one putative signature of consciousness, the P300, has been reported in response to stimuli.

Outstanding questions then remain: are external stimuli so deeply processed that they can access consciousness during sleep? If not, how deeply this information is processed? Experiments on external information processing during sleep are relatively rare, and they do not bring understandable explanation as to why a given stimulus may be processed or not. My goal was then to further understand:

- How deeply can the brain process external information during sleep? And especially,
- What are the underlying functional mechanisms responsible for residual processing or their abolition?

I.6.2. Originality of the present work and methodological considerations

I tackled this old question of the processing depth during sleep because I capitalized on two major methodological points that could bring new insights compared to previous studies. First, we used magnetoencephalography (MEG) in addition to EEG for recording subjects. Second, we approached the question through hierarchical predictive coding mechanisms.

MEG recordings during sleep

During sleep, information related to external stimulations is often tricky to detect in EEG, due to ongoing spontaneous oscillations and large amplitude slow waves. Also, EEG patterns are largely spread over the scalp leading to imperfect spatial resolution. I therefore chose to combine MEG with EEG to record brain activity of sleeping subjects, taking advantage of its better signal-to-noise ratio and its better spatial resolution, still benefiting from high temporal resolution with a recording sample time every millisecond. This methodological point is a strong force and originality in our work, as all previous studies interested in our topic only recorded EEG or fMRI signals.

The MEG (Elekta neuromag) used in this work has 306 sensors (102 magnetometers, 102 planar gradiometers and 102 gradiometers), which confer a high spatial covering over the scalp. In addition, magnetic fields are less distorted than electric fields by the skull and scalp, which results in a better spatial resolution of the MEG (Cohen and Cuffin 1983), and enable to perform much more accurate source reconstructions. Also, those two methods bring complementary information, as the EEG measures both radial and tangential components of current sources, while the MEG is only sensitive to the tangential ones, but which will be better recorded as not obscured by radial sources (Cohen and Cuffin 1983; Lopes da Silva et al. 1991).



Figure 27. MEG set up

I then needed to adapt MEG recordings for sleep studies. To give a brief overview of the procedure, subjects were recorded in the MEG shielded room in a bed (with pillows and cover) placed in front of the MEG in supine position. EEG signals were recorded with the built-in Elekta EEG system of 60 electrodes, which was positioned on the subject' scalp before he entered in the MEG room. Additional individual electrodes were placed in order to record ECG, EOG (2 horizontal and 2 vertical), and thin EMG to complete polysomnographic recording in order to be able to score sleep stages (EEG+EOG+EMG) and to remove ECG and EOG artifacts. Note that during acquisition, head position relative to the MEG helmet was continuously recorded (for subsequent realignment) and EEG and MEG signal were monitored on line. The realignment between MEG sensors and the head position during preprocessing ensured the accurate correspondence between sensors and brain signals through the experiment. Actually, the degree of freedom of the head in the helmet was quite limited with the head on the headrest, and movements were very limited.

Subjects were recorded during a nap. In order to major chances to have them sleeping in the MEG, sleep restriction (4 hours of sleep) was applied the night before (controlled by actimetry). The nap was done in the morning to increase chances to record REM sleep, as predicted by circadian regulation.

Sleep data were analyzed as in wakefulness, with a high-pass filter at 0.3 Hz to remove very slow oscillations as dermogram that could occur during sleep. We did not remove sleep spindles from analysis, despite knowing that they may decrease information integration through the cortex. In fact, unlike spindles in EEG, spindles in MEG are mostly local in various areas of the brain, and then removing each trial containing a spindle would lead to end with very few trials. Also, spindles recorded in EEG were not automatically recorded in MEG and vice versa (they even have been suggested to emerge from different sources of the thalamo-cortical system (Dehghani et al. 2010)). Considering K-complexes, they were removed from analysis because we used repetitive auditory stimulations with very short intervals so that we could not clearly distinguish evoked from spontaneous K-complexes.

Assessing predictive coding capabilities of the sleeping brain

In addition to imaging methods, I used a novel approach in regards to previous sleep studies, with new paradigms that enabled to investigate underlying mechanisms generating brain potentials and to test information integration through the brain hierarchy. I focused on hierarchical predictive coding capabilities of the sleeping brain.

Predictive coding is an efficient way to code information that is believed to be a major operating mode of the brain (Friston 2005). In order to minimize costs and energy, given the extreme redundancy of information in the environment, the brain learns about invariants and generates internal

models of the world. It can then elaborate predictions about incoming sensory inputs, and only encode new information if the inputs violate its predictions, so that the model can be up-dated. This predictive system relies on a hierarchical organization between feedforward connections that mediate prediction error signals from lower to higher areas, which in turn send backward information about predictions. The cortex has this hierarchical organization, within each cortical column and through brain areas, and predictions occur at many if not all steps of the cortical hierarchy.

Testing different hierarchical levels of predictions is then an interesting way to assess the steps at which information is integrated or disrupted during sleep.

I.6.3. Outlines of the thesis

In the following chapter (chapter II), I first assess the capacity of the sleeping brain to detect auditory novelty. We saw that if the sleeping brain appears capable of detecting simple deviant sounds, previous studies were not able to reveal underlying mechanisms and to dissociate passive bottom-up sensory processes from active top-down ones. Using two original paradigms embedding different hierarchical levels of temporal auditory regularities, I demonstrate that both high-level (P300) and low-level (MMN) top-down predictions are abolished during sleep, in NREM as in REM sleep, while bottom-up sensory adaptation is preserved. I also bring new evidence on the association of the P300 with external awareness and demonstrate its loss during sleep, and clarify the functional significance of the MMN in term of prediction and adaptation processes.

As abstract temporal regularities are only passively processed during sleep, I tackled in chapter III the question of the processing depth of external stimuli that refer to knowledge already stored in long term memory. Using simple arithmetic facts, I show here that the sleeping brain is able to make the difference between correct and incorrect results, thus revealing that error signals can be elicited by the sleeping brain in the context of over-learned knowledge.

II. DISRUPTION OF HIERARCHICAL PREDICTIVE CODING DURING SLEEP

II.1. Abstract

When presented with an auditory sequence, the brain acts as a predictive-coding device that extracts regularities in the transition probabilities between sounds and detects unexpected deviations from these regularities. Does such prediction require conscious vigilance, or does it continue to unfold automatically in the sleeping brain? The Mismatch Negativity (MMN) and the P300 components of the auditory event-related potential, which reflect two steps of auditory novelty detection, have been inconsistently observed in the various sleep stages. To clarify whether these steps remain during sleep, we recorded simultaneous electro and magneto-encephalographic signals during wakefulness and during sleep in normal subjects listening to a hierarchical auditory paradigm including short-term (local) and long-term (global) regularities. The global response, reflected in the P300, vanished during sleep, in line with the hypothesis that it is a correlate of high-level conscious error detection. The local mismatch response remained across all sleep stages (N1, N2 and REM sleep), but with an incomplete structure: compared to wakefulness, a specific peak reflecting prediction error vanished during sleep. Those results indicate that sleep leaves intact initial auditory processing and passive sensory response adaptation, but specifically disrupts both short-term and long-term auditory predictive coding.

II.2. Introduction

Sleep is regarded as a state of unconsciousness of the environment in which behavioral responses to external stimuli are drastically reduced (Rechtschaffen et al. 1966). Yet the depth at which sensory information remains processed during sleep, and the precise stage at which processing is disrupted, remains uncertain. An early theory for the reduced responsiveness to external stimuli during sleep is the thalamic-gating hypothesis (Steriade et al. 1993b). According to this theory, tonic and synchronous thalamic activity during sleep would disrupt the information transmission from the sensory periphery to the cortex. Alternatively, it has been proposed that sleep may induce a loss of integration at a late stage of cortical processing (Massimini et al. 2005; Horovitz et al. 2009; Tagliazucchi et al. 2013b). Indeed, preserved activation of primary sensory cortices has been reported

in electrophysiological studies in animals (Peña et al. 1999; Edeline et al. 2001; Issa and Wang 2008; Nir et al. 2013) and in neuroimaging studies in humans (Portas et al. 2000; Czigic 2002b; Dang-Vu et al. 2011). Furthermore, stimuli that have behavioral relevance, such as hearing one's name, may induce a broad spread of activation into higher cortical areas (Portas et al. 2000) and evoke late scalp event-related potentials (ERPs) (Bastuji et al. 2002).

In addition to relevance, novelty may also be a significant factor that modulates the propagation of auditory signals during sleep. In the awake state, presenting a novel deviant sound in a sequence of repeated standard ones, the so-called oddball paradigm, elicits a series of novelty-related ERPs. The mismatch negativity (MMN) is a fronto-central negative component peaking around 100-250ms after deviant tones (Näätänen et al. 2007) which arises from auditory areas (Näätänen et al. 2001). The P3b or P300 is a slower sustained posterior positivity elicited around 300ms (Sutton et al. 1965), which is thought to arise from recurrent interactions in a broad set of interconnected areas including fronto-parietal cortices (Dehaene and Changeux 2011). Those two potentials are interpreted as neural correlates of two different hierarchical stages in the process of novelty detection. According to the predictive coding hypothesis (Friston 2005), the laminar organization of the cortex enables the formation of internal models of increasing degree of abstraction at successive levels of the cortical hierarchy. Each model extracts regularities from its bottom-up sensory inputs at a given time scale, and uses these regularities to generate top-down predictions which are compared with subsequent inputs. A sound that violates a learned regularity will thus generate an error signal, which can be used to readjust the model.

Within this framework, the P300 is considered as a high-level prediction error signal associated with conscious novelty detection, which is strongly reduced in various non-conscious conditions such as coma or anesthesia (Plourde 1991; Koelsch et al. 2006; Bekinschtein et al. 2009; Dehaene and Changeux 2011), while the MMN is regarded as a lower-level pre-attentive prediction error signal (Garrido et al. 2009; Farley et al. 2010; Todorovic and de Lange 2012; Wacongne et al. 2011; Wacongne et al. 2012), which may be generated non-consciously (Näätänen et al. 2001). In fact, two distinct mechanisms are involved during the MMN time window: an active predictive mechanism (MMN proper), and a passive habituation phenomenon called stimulus specific adaptation (SSA). SSA follows the repetition of a sound and leads to reduced neural responses. It is theorized that, when a rare sound occurs, the activation of a set of non-adapted "fresh afferents" generates a recovery of the original neural response. Inasmuch as SSA reduces the impact of redundant sensory inputs, it might itself be considered as a primitive predictive device, yet one that rests only on neurotransmission mechanisms local to each neuron (Fiorillo 2008). It was initially thought that passive SSA may account for the MMN (Ulanovsky et al. 2003; May and Tiitinen 2010), but there is now evidence that the latter involves active predictive-coding mechanisms (Garrido et al. 2009; Farley et al. 2010; Todorovic and de Lange 2012; Wacongne et al. 2011; Wacongne et al. 2012). To summarize, at least

three successive brain responses to novelty exist: recovery from sensory adaptation, MMN in the proper sense, and P300.

The present study aims to clarify whether the non-conscious sleeping brain remains able to detect auditory novelty, and whether predictive coding and habituation mechanisms continue to operate during sleep. Previous EEG experiments searching for MMN and P300 responses during sleep have yielded partially contradictory results (Atienza et al. 2001; Cote 2002; Ruby et al. 2008b), in part because EEG measures were affected by uncontrolled noise arising from sleep signals and EEG artifacts. Moreover, the classical oddball paradigm used in these studies did not clearly dissociate the various hierarchical levels of novelty detection. In this paradigm, the late P300 component (P3b) may be confounded with another lower-level positive component (P3a) that arises automatically shortly after the MMN (Faugeras et al. 2012). Furthermore, many oddball paradigms fail to dissociate prediction from adaptation: the deviant sound exhibits both a low absolute frequency and a low transition probability relative to preceding sounds, leading to violations of both adaptation and prediction.

Here, we obtained simultaneous electro- and magneto-encephalography recordings (EEG/MEG) during wakefulness and during non-rapid-eye-movement (NREM) and rapid-eye-movement (REM) sleep, thus affording better signal-to-noise ratio and spatial resolution than previous EEG recordings. In experiment 1, to probe the hierarchy of novelty detection processes, we used the local/global paradigm, a variant of the oddball paradigm that disentangles the MMN and the P300 (Bekinschtein et al. 2009). This paradigm comprises two nested levels of temporal regularities, a short time-scale structure, termed ‘local’, and a longer time-scale structure, termed ‘global’ (Fig. 1). Violations of local regularities elicit MMN/P3a responses, while violations of global regularities elicit a P300 response (Bekinschtein et al. 2009; Wacongne et al. 2011). In patients with disorders of consciousness (DOC), this paradigm successfully dissociated conscious from non-conscious states based on the presence or absence of the P300 following global violations, while the MMN remained present under non-conscious conditions (Bekinschtein et al. 2009; Faugeras et al. 2012; King et al. 2013a; Sitt et al. 2014). Using the local-global paradigm during sleep should dissociate high-level predictive coding reflected in the P300 from lower-level prediction or adaptation effects reflected in the MMN. To further disentangle prediction from adaptation, in experiment 2 we used an aBaBa paradigm in which the two mechanisms work in opposite ways: predictive coding induces a mismatch response to rare stimulus repetitions (aa), while sensory adaptation induces an enhanced response to stimulus alternations (aB) (Horváth and Winkler 2004; Wacongne et al. 2012).

II.3. Results

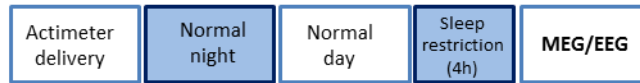
In experiment 1, M/EEG data were collected before sleep ($Wake_{PRE}$), during a morning nap (N1, N2 and REM sleep stages), and after awakening ($Wake_{POST}$). During N1 sleep, as they fell asleep, subjects still occasionally responded to global deviants, allowing us to retrospectively split the data into N1-responsive and N1-non-responsive states. The total number of subjects in each sleep stage varied depending on the number of subjects who reached each stage and on the quality of their data (see methods).

II.3.1. Local effect: disruption of the mismatch response (MMR) during sleep

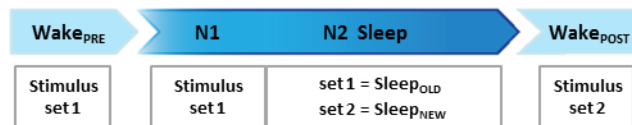
Violations of short-term regularities were analyzed by comparing responses to local deviant and local standard sequences, a contrast termed the local effect (Fig. 28). Using sensor-level statistics, a significant local effect was found across all analyzed states of vigilance, from wakefulness to N2 and REM sleep (Fig. 29A). However, the brain response to deviant tones was deeply modified in sleep as compared to wakefulness.

During the $Wake_{PRE}$ session, local deviants elicited a MMR over temporal MEG sensors, characterized by 3 successive steps of auditory processing (Fig. 29C): an early deflection (left temporal cluster, 48-100ms, $p < 0.05$), an intermediate effect of reversed polarity peaking around 150ms (120-176ms, $p < 0.01$), and a late effect spreading from temporal toward anterior areas (left temporal-anterior cluster: 240-498ms, $p < 0.001$). In EEG (Fig. 29D) the local effect led to a characteristic MMN: a negative deflection at the vertex around 150ms associated with a polarity inversion at the mastoids (128-176ms, $p < 0.05$). It was followed by a positivity over fronto-central areas later turning into a broad centro-parietal positivity, compatible with P3a/P3b waves (224-448ms, $p < 10^{-4}$). Only the early effect (before 100ms) failed to be detected in EEG during wakefulness, despite the significant early deflection visible in MEG. Considering the better signal-to-noise ratio in MEG compared to EEG and for better readability, the following results and statistical analyses are reported only for MEG data (planar gradiometers type 2, see supplementary methods). Results for all types of sensors are shown in Fig. 34.

A. Protocol

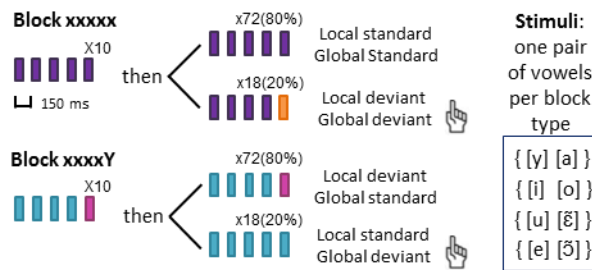


B. Procedure during MEG/EEG recording



C. Block types and Stimuli

Stimulus set 1 = 2 xxxxx + 2 xxxxY blocks with 2 pairs of vowels
Stimulus set 2 = 2 xxxxx + 2 xxxxY blocks with 2 **new** pairs of vowels



Task = motor response to global deviants

Local mismatch effect = Local deviants – Local standards

Global deviance effect = Global deviants – Global standards

Figure 28. Experimental protocol.

A. Sleeping in the MEG was facilitated by sleep restriction during the previous night, as controlled by actimetry. **B.** Recordings were obtained during three sessions with auditory stimuli: before (Wake_{PRE}), during (Sleep), and after the nap (Wake_{POST}). The goal was to evaluate whether the brain reacts to local and global novelty during sleep, and to test whether those effects depend on having previously heard the stimuli in the waking state or whether they can be acquired during sleep. A first set of 4 blocks was presented during Wake_{PRE} (stimulus set 1), then again while subjects fell asleep (N1 sleep). When subjects reached stage 2 (N2 sleep), in addition to stimulus set 1, a set of 4 new blocks with new stimuli was introduced (stimulus set 2). The corresponding datasets were called Sleep_{OLD} and Sleep_{NEW}. Finally, stimulus set 2 was again presented during Wake_{POST}. **C.** Sequences with five identical vowels were termed “local standards”, and sequences in which the fifth vowel was different (thus generating a local mismatch effect) were termed “local deviants”. In each block, one sequence (local standard in aaaaa blocks or local deviant in aaaab blocks) was selected and was repeated 10 times then on 80% of the trials, thus establishing a “global standard”. The other sequences (respectively local deviant or local standard), termed “global deviant”, were presented on the remaining 20% of trials (thus generating a global deviance effect). Subjects were asked to press a button to global deviants in half of the blocks during Wake_{PRE} and Wake_{POST}, and whenever they were aware of them during the Sleep session.

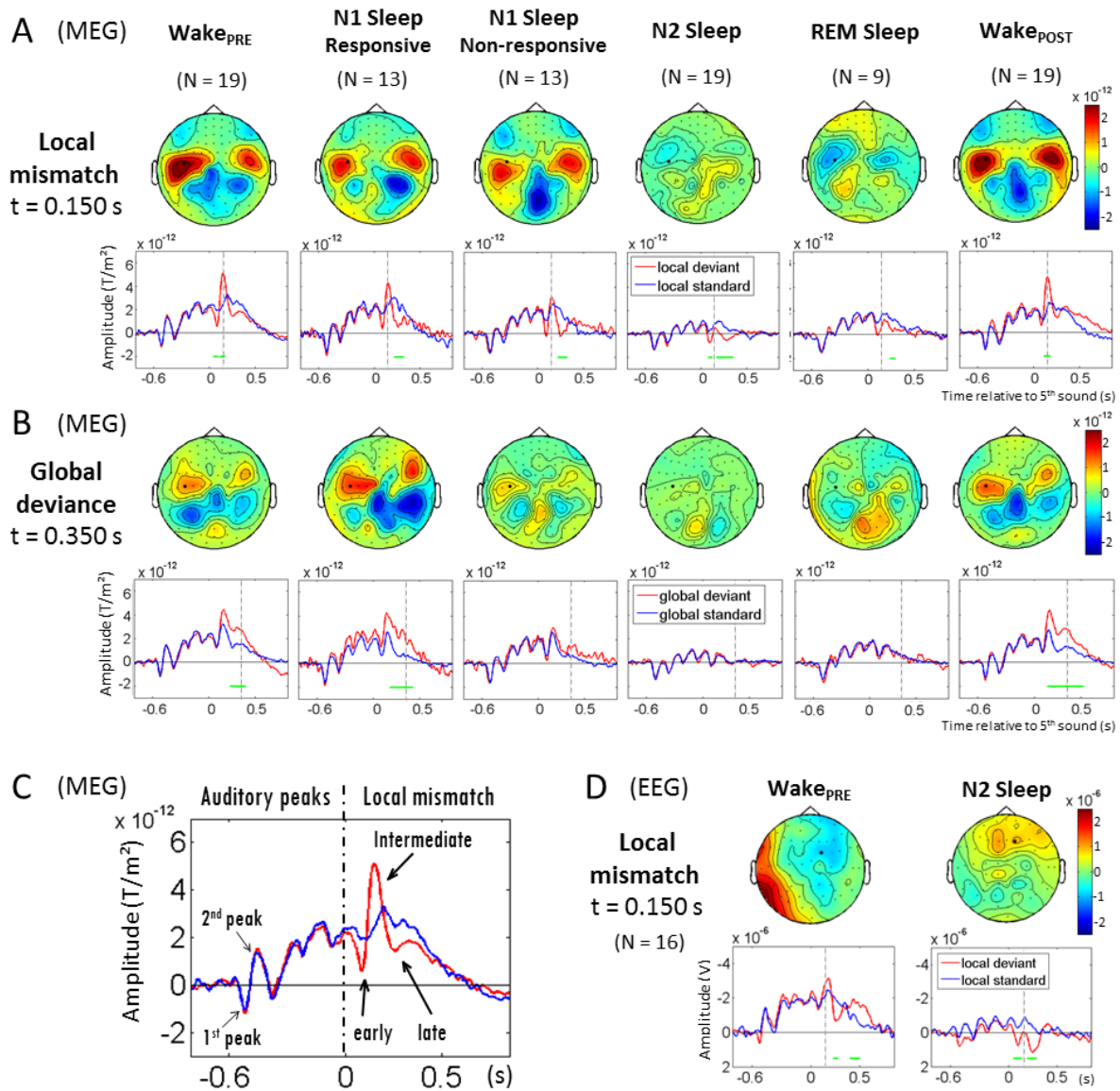


Figure 29. Event-related responses to local and global novelty as a function of vigilance states.

A. Local mismatch response in MEG. Topographies of the local effect (local standards - local deviants) are shown at $t=150\text{ms}$ after the fifth sound. ERF are shown for local standard and local deviant sequences at one left temporal MEG sensor (black dot, same sensor across states). Cluster-based significant effects ($p < 0.05$ corrected) at this sensor in a $48 - 498\text{ms}$ time-window are represented by green lines. The local mismatch effect is partially preserved across all sleep stages, yet its sharpest central peak, present during wakefulness, progressively vanishes during sleep. **B.** Global deviance response in MEG. Topographies of the global deviance effect (global deviants - global standards) are shown at $t=350\text{ms}$ post fifth sound. ERF are shown for global standard and global deviant sequences at the same left temporal MEG sensor (black dot). Significant effects at this sensor in a $50 - 700\text{ms}$ time-window are shown (green lines). The global effect (P300) is found when subjects are awake, both in Wake_{PRE} and $\text{Wake}_{\text{POST}}$. It remains present during N1-sleep when subjects are behaviorally responsive, but disappears as soon as subjects become unresponsive and in all sleep stages. **C.** Visualization of the first MEG auditory evoked peaks and decomposition of the MEG local mismatch effect into three components during wakefulness (Wake_{PRE}): the early effect before 100ms , the intermediate effect of inverse polarity around 150ms , the late effect after 200ms . **D.** Local mismatch in EEG, during Wake_{PRE} and N2 sleep. Topographies are shown at 150ms . The MMN at 150ms in Wake_{PRE} , contemporaneous of the MEG intermediate effect, vanishes during sleep.

During sleep, the early MMR was observed in all sleep stages, but reached significance only in N2-Sleep (Sleep_(OLD+NEW)): 76-128ms, $p < 0.05$), where its amplitude was slightly larger than in the other sleep stages (Table S1a). Crucially, the intermediate effect was missing: its amplitude decreased progressively with the depth of sleep, failing to reach significance from N1-responsive sleep (Fig. 29A and 29D) and creating a significant difference with the wake period (see Table S1b). The late effect, however, was found in all sleep stages (N1-responsive and non-responsive: 220-348ms, $p < 0.01$; N2: 136-356ms, $p < 0.001$; REM: 236-296ms, $p < 0.05$), without any difference in amplitude (Table S1c).

During wakefulness in the Wake_{POST} session, the MMR recovered virtually the same shape as prior to sleep (Fig. 29A). The early effect failed to reach significance, but the intermediate effect recovered over temporal sensors (left temporal cluster: 116-184ms, $p < 0.05$) and the late effect was significantly detected over the right temporal-anterior sensors (216-324ms, $p < 0.05$). When comparing Wake_{PRE} and Wake_{POST}, activations differed only during the late time-window over the right temporal region, where they were slightly stronger for Wake_{POST} (216-332ms, $p < 0.05$). Given such minimal differences, we grouped Wake_{PRE} and Wake_{POST} conditions in subsequent figures and analyses.

To test the acquisition of new regularities during sleep, new vowel sequences were introduced during N2 sleep (N2-Sleep_{NEW}) along with sequences already heard during wakefulness (N2-Sleep_{OLD}). The early effect was not detected by cluster analysis for Sleep_{OLD} and Sleep_{NEW} data separately. However, its amplitude was significantly larger for Sleep_{NEW} than for Sleep_{OLD} stimuli when comparing them with a paired Wilcoxon test (Table S1a). No intermediate effect was found in either condition (Fig. 29A). In N2-Sleep_{OLD}, the late effect was detected over left temporal sensors from 176 to 220ms ($p < 0.05$). In N2-Sleep_{NEW}, the late effect was also detected over left temporal sensors (176-320ms, $p < 0.05$), with a slightly different topography spreading over postero-median (92-312ms, $p < 0.01$) and then anterior sensors (300-406ms, $p < 0.01$). The direct comparison in cluster analysis between Sleep_{OLD} and Sleep_{NEW} stimuli revealed a significant interaction in the postero-median region (88-308ms, $p < 0.05$).

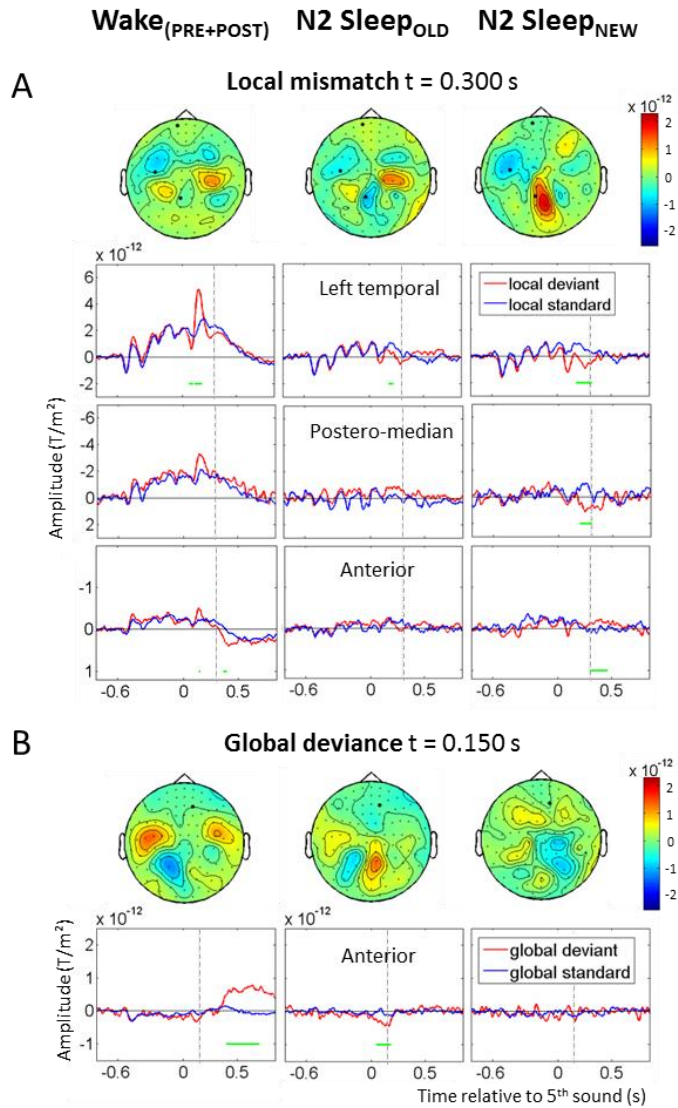


Figure 30. Effects of prior exposure to sound sequences on the responses to local and global novelty.

Each column presents the data from a specific state of vigilance and stimulus set: Wake_(PRE+POST) (left column), N2-Sleep_{OLD} (middle column) and N2-Sleep_{NEW} (right column). **A.** Local mismatch effect over left temporal, postero-median and anterior MEG sensors. Cluster-based significant effects ($p < 0.05$) are represented by green lines. Topographies are shown at 300ms, when activations between Sleep_{OLD} and Sleep_{NEW} significantly differ. In Wake_(PRE+POST), the early and intermediate effects are visible in the left temporal region ($p < 0.01$), while the late effect only reaches significance in more anterior areas. In Sleep_{OLD} the significant mismatch effect is limited to a transient late effect over temporal regions ($p < 0.05$). In Sleep_{NEW}, when new vowels are introduced during sleep, the late novelty response is enhanced and spreads over postero-median ($p < 0.01$) and anterior areas ($p < 0.01$). **B.** Global effect over anterior MEG sensors. Topographies are shown at 150ms, when activations between Sleep_{OLD} and Sleep_{NEW} significantly differ. In Wake_(PRE+POST), the effect over anterior sensors is large and sustained after 400ms ($p < 0.01$). In Sleep_{OLD}, with sequences previously heard during wakefulness, an early transient effect is found ($p < 0.01$). No global effect is found for Sleep_{NEW}.

Distributed cortical sources for these effects were computed in Wake_(PRE+POST), N2-Sleep_{OLD} and N2-Sleep_{NEW} conditions (Fig. 3&, left). In all conditions, the early local effect was bilateral and localized in the vicinity of auditory cortices (Wake: max. at 84ms, MNI coordinates: -56 -16 13; Sleep_{OLD}: max. at 104 ms, MNI: -49 -16 15; N2-Sleep_{NEW}: max. at 104ms, MNI: -47 -36 12). The intermediate effect, however, was visible only during Wake. It was characterized by strong activations in auditory cortices (max. at 148ms, MNI: -52 -36 15) alongside a larger network including inferior frontal gyrus, left para-hippocampus and precuneus. During the late effect, activations during Wake remained sustained in peri-auditory areas (max. at 252ms; MNI: 44 -32 18) and also expanded into broader associative areas (posterior and superior cingulate, insula, parietal lobe and middle frontal gyrus; see Fig. 30). During sleep, only a subset of these areas remained responsive, at a much lower level, at the time of the late effect (Sleep_{OLD} : superior temporal and supramarginalis gyri, right insula, parietal lobe, posterior superior frontal gyrus and superior cingulate; Sleep_{NEW} : bilateral superior temporal and supramarginal gyri and right superior cingulate). Compared to Sleep_{OLD} and to Wake, Sleep_{NEW} led to additional late activations in the precuneus (max. at 240ms, MNI: 20 -57 23).

To further assess the similarity of the local novelty response during wakefulness and during sleep, we used multivariate classification. Within each subject, we trained a decoder to classify each trial as local standard or local deviant at each time point, using the Wake_{PRE} data for training and then testing for generalization to other states of vigilance. This method increases signal-to-noise ratio, takes into account inter-individual variability, and provides a stringent test of the similarities of brain activity patterns across conditions, even in the presence of time delays (King and Dehaene 2014; King et al. 2014).

The local classifier trained and tested within the Wake_{PRE} session achieved significant decoding scores from 76 to 620ms ($p < 0.05$), covering early, intermediate and late MMR effects (Fig. 31A, Left). The same classifier also generalized fully to the Wake_{POST} session, with results virtually identical to Wake_{PRE} (Fig. 5A, Left). But tested on N2-Sleep, the classifier generalized only during the early and late effects (76-100 and 212-588ms, $p < 0.05$). Strikingly, the ~150-ms peak during which excellent decoding was achieved for Wake data (AUC ~ 0.80) did not generalize at all to sleep (AUC not significantly different from 0.5). Comparing the generalization scores from Wake_{PRE} to Sleep and from Wake_{PRE} to Wake_{POST} confirmed a significant difference from 116ms to 484ms (Wilcoxon sign rank test, $p < 0.05$). This was not due to an absence of novelty response during sleep in the intermediate time period because when the classifier was trained and tested within the N2-Sleep_(OLD+NEW) dataset (Fig. 31C, Left), it performed successfully above chance from 108 to 172ms ($p < 0.05$). These results indicate that the nature and topography of the novelty response during the intermediate time window in wakefulness differed from those observed during sleep, such that no generalization was possible from one to the other. Similar results were obtained when computing the full temporal generalization

matrix (Fig. 35), and also when analyzing separately the N2-Sleep_{OLD} and N2-Sleep_{NEW} trials (Fig. 31B, Left).

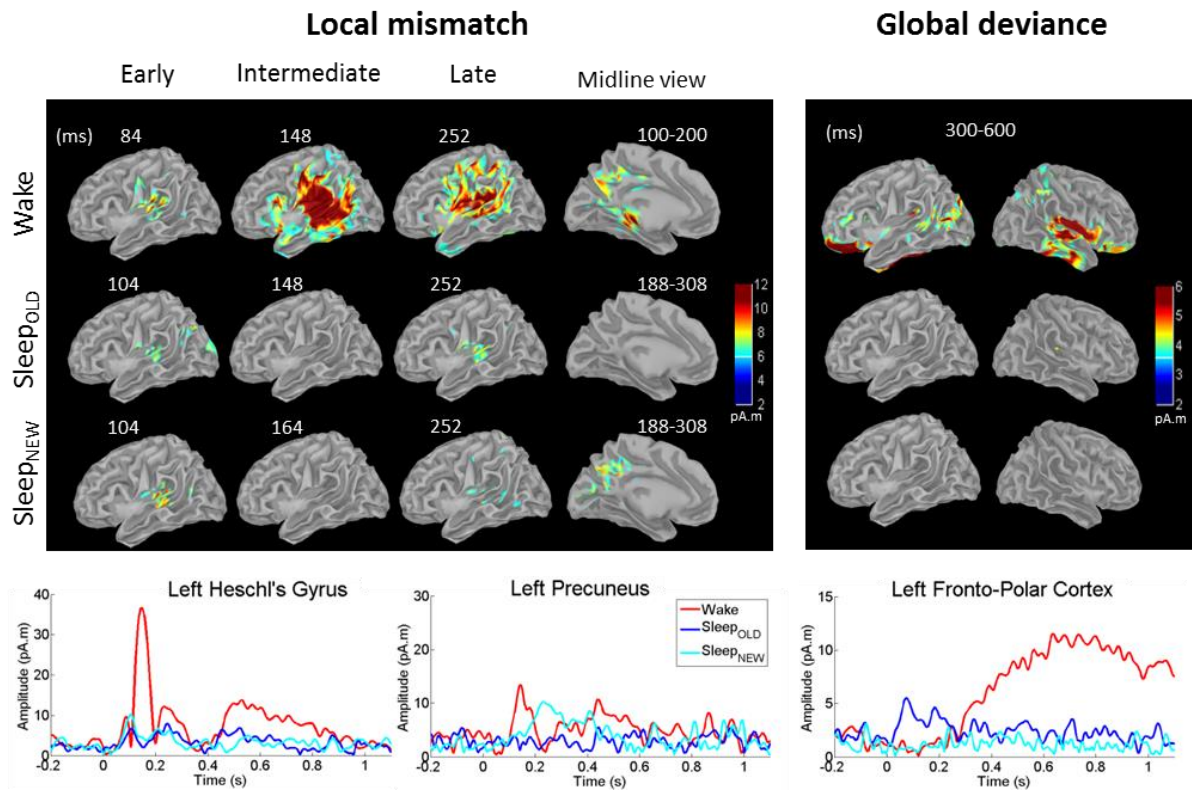


Figure 31. Source reconstructions.

Colors represent the intensity of estimated source currents in pA.m. Time series represent the time course of the absolute value of source current in specific regions of interest. Left. Local mismatch. Auditory cortices respond with a slight delay during N2 sleep. Intermediate-latency activations vanish during sleep. A late effect is present during sleep, although attenuated in amplitude, and with a delayed activation of the precuneus only for new stimuli. Time series are presented for the left Heschl's gyrus and the precuneus. Right. Global deviance. During wakefulness, broad parietal, frontal and temporal activations are present. During sleep, this activity vanishes, except for an early transient activity for old stimuli previously heard during wakefulness as seen on time series (N2-Sleep_{OLD}).

II.3.2. Global effect: loss of the P300 during sleep

We next investigated the response to global novelty, i.e. the difference between rare and frequent sequences of five sounds. During wakefulness (Wake_{PRE} and Wake_{POST}, Fig. 29B), global deviants were followed by sustained activations, starting over temporal sensors, then spreading towards anterior regions (left anterior temporal cluster, Wake_{PRE}: 232-700ms, $p < 10^{-4}$; Wake_{POST}: 144-

700ms, $p < 10^{-4}$). Similarly, EEG recordings revealed a posterior positivity (Wake_{PRE}: 256-700ms, $p < 10^{-4}$; Wake_{POST}: 136-680ms, $p < 0.01$) with the characteristics of a classical P300 (Fig. 35). The comparison between Wake_{PRE} and Wake_{POST} revealed stronger sustained MEG activations in anterior areas during Wake_{PRE} (596-672ms, $p < 0.05$), despite similar amplitudes in auditory areas (Table S2). In N1 sleep when subjects were still responding, the global effect continued to be elicited over temporal and anterior regions (N1-responsive: 176-700ms, $p < 10^{-4}$). Critically however, even during N1 sleep, as soon as subjects ceased to be behaviorally responsive, the P300 vanished (N1-non-responsive, Fig. 29B). In N2 sleep and in REM sleep, subjects did not respond behaviorally to any global deviant, and no response to global deviance was seen (for ERPs and all MEG sensors results see Fig. 35). Note that in a recent study, Kouider et al. (Kouider et al. 2014) detected markers of motor preparation (lateralized readiness potentials; LRPs) in the descent to sleep, even in the absence of behavioral responses. In the present case, subjects made only unimanual responses, and therefore we could not compute LRPs. Thus, we cannot exclude the possibility of an automatic motor initiation during sleep, but can only conclude to the absence of the P300 associated with the global effect.

When analyzing separately the old and new stimuli, an early and transient global effect to old stimuli was found over anterior sensors in N2 Sleep (N2-Sleep_{OLD}: 48-188ms, $p < 0.01$). No such activation was found for new stimuli introduced during sleep (N2-Sleep_{NEW}, Fig. 30B). The direct comparison between N2-Sleep_{OLD} and N2-Sleep_{NEW} stimuli revealed a significant interaction in the same anterior sensors (68-168ms, $p < 0.05$). Note that during wakefulness an early effect in those regions fell just short of significance (Wake_(PRE+POST): 88-152ms, $p = 0.05$).

In source reconstructions, the global effect during Wake comprised a first set of activations mainly localized to auditory areas (max. at 144ms in the right superior temporal gyrus/planum temporale, MNI: 32.46 -26.02 10.34), associated with activations in the bilateral precuneus, parahippocampal gyri, and the posterior cingulate. It was followed by large and sustained activations in associative cortices (temporal and parietal lobes, right insula, posterior and superior cingulate cortex, dorso-lateral prefrontal and lateral orbito-frontal cortices; Fig. 31, right). No such activation was found during sleep. However in N2-Sleep_{OLD}, an early and transient activity was found in fronto-orbital areas, followed by small activations of the right supramarginal gyrus (140-340ms).

In multivariate classification, the global effect was successfully decoded during Wake_{PRE}, with almost complete generalization to Wake_{POST} (Fig. 32A, right). Note that the effect was just above chance even before the onset of the fifth sound, an effect observed in previous work (King et al. 2013a) and linked to the anticipation of global deviants sequences, as their probability of occurrence increases with the successive presentation of global standards. None of these effects generalized to Sleep data (figure 32A). When testing the generalization from Wake_{PRE} to N2-Sleep_(OLD+NEW), only a very transient generalization was seen from 212 to 228ms (Fig. 32A, right). This effect was due to a transient period of generalization (196 to 252ms, $p < 0.05$) for N2-Sleep_{OLD} stimuli only (Fig. 32B,

right). No generalization was possible from Wake_{PRE} to N2-Sleep_{NEW} stimuli. Even when trained and tested specifically on Sleep_(OLD+NEW) dataset, the classifier was unable to classify correctly global deviant versus global standard sequences (Fig. 32C, right). These results suggest that during sleep, the brain is not responsive to global regularities, except for a transient period unique to previously learned stimuli.

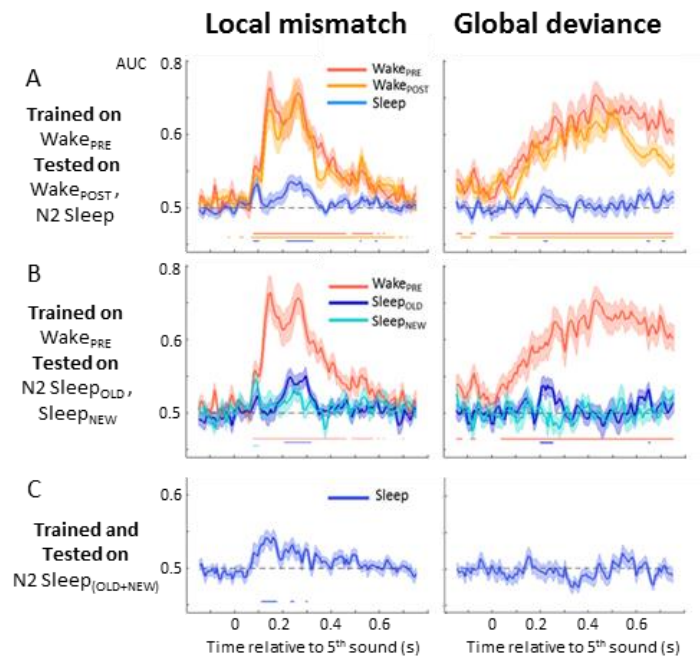


Figure 32. Decoding the brain's novelty responses to local mismatch and to global deviance during wakefulness and N2 Sleep.

At each time point, multivariate classifiers were trained to discriminate either local standards from local deviants (xxxxx versus xxxxY series, left column), or global standard from global deviants (frequent versus rare series, right column). Each curve represents the area-under-the-curve (AUC), a parameter-free measure of decoding success (chance level=0.5). Significant decoding ($p < 0.05$) is shown by a horizontal line. **A.** Generalization from Wake to Sleep. A classifier was trained on the Wake_{PRE} session and its ability to accurately classify Local (left panel) and Global (right panel) effects was tested on the same session (red), on Wake_{POST} (orange) and on N2-Sleep_(OLD+NEW) (blue). **B.** Improved generalization for stimuli previously heard during wakefulness. A classifier was trained on Wake_{PRE} and tested separately on Sleep_{OLD} (dark blue) and Sleep_{NEW}(cyan). **C.** Decoders trained during sleep. A classifier was trained and tested on the N2-Sleep_(OLD+NEW) dataset.

II.3.3. Modulation of evoked responses across vigilance states

Beyond the evoked responses to auditory novelty, our paradigm also provided basic data on the evolution of auditory responses evoked by the first four sounds across the different states of vigilance. A clear dissociation was seen as a function of the latency of auditory responses (Fig. 29).

The amplitude of the first measurable response to sound onset (first peak in Figure 29C) remained unchanged across sleep stages (see supplementary Table S3a for full statistics), although its latency significantly increased (Wake = 73.4ms, N1=81.5ms, N2 = 100.4ms, REM = 94.2ms). The next peak (second peak in Figure 29C), however, was dramatically reduced in amplitude during N1, N2 and REM sleep, and its latency also increased (wake = 158.2ms, N1=176ms, N2 = 179.8ms, REM = 183.6ms; Table S3b).

Because the temporal profile and topography of this second peak were similar to those of the local mismatch response, and because both components decreased during sleep, we examined if these two phenomena were related across subjects. A regression analysis indeed revealed a positive correlation between the amplitudes of this second peak and of the intermediate MMR during N2 sleep ($r=0.53$, $p<0.05$). Thus, the reductions of the second auditory peak and of the MMR were related phenomena.

After the second sound, it became harder to separate the peaks evoked by individual stimuli, but the overall envelope of responses was also strongly diminished during sleep (Fig. 29). In the local-global paradigm with awake, conscious subjects, a progressive ramping-up of brain responses across the four sounds has been described and tentatively ascribed to an expectation of the final sound (Chennu et al. 2013). We verified that this ramping-up was present in our data during wakefulness (cluster analysis for slope different from 0, $p<0.001$ in temporal areas), and that it diminished during N1 and then N2 sleep (Table S4), while remaining significant (significant slope in N2 sleep, $p<0.001$). A slight rebound was observed during REM sleep, with an effect size indistinguishable from N1 sleep.

II.3.4. Separate assessment of predictive coding and sensory adaptation

Experiment 1 yielded a clear-cut vanishing of the global effect during sleep, but the results for the MMR were more ambiguous: a significant difference continued to be observed between local deviants and local standards, yet the main peak of the MMR decreased during N1 and vanished during N2 and REM. Because this main peak has been associated with prediction error in previous studies (Wacongne et al. 2011; Wacongne et al. 2012; Todorovic and de Lange 2012), one hypothesis is that sleep selectively disrupts predictive coding and preserves only sensory adaptation. To evaluate this possibility, we ran a second experiment where sensory adaptation and predictive coding were independently manipulated (Fig. 6). We replicated the aaaaa blocks, where rare ‘aaaaB’ deviant sequences violate both prediction and adaptation. We also introduced novel blocks using aBaBa and aBaBB sequences, in which the dominant expectation is an alternation of the two sounds. Here, predictive coding should induce a prediction-error response to the final unexpected sound repetition in aBaBB, whereas passive adaptation makes the opposite prediction of a reduced activation to repetition (or no effect at all if a single stimulus repetition fails to yield a significant adaptation).

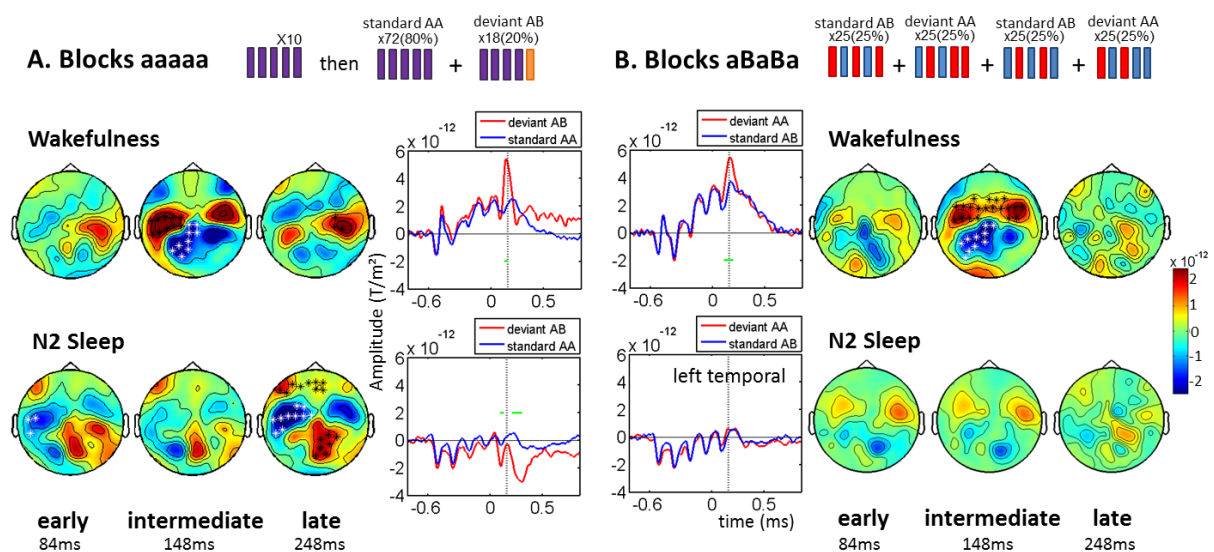


Figure 33. Dissociation between disrupted predictive coding and preserved sensory adaptation during sleep.

A. Blocks aaaaa: replication of experiment 1. During wakefulness, aaaaB deviants that violate both prediction and adaptation elicited a MMR with three components (early, intermediate and late). During N2 sleep early and late components remained present, but the intermediate component vanished. B. Blocks aBaBa: dissociation of prediction and adaptation. During wakefulness, the aBaBB deviants that violate prediction but not adaptation elicited a MMR during the intermediate time period only. During N2 sleep, no significant difference remained. Topographies for each components are shown, with significant clusters (* $p < 0.05$). ERF time series with significant activations for the left temporal MEG sensor are displayed (horizontal green lines). The vertical dotted line marks the peak of the intermediate effect (148ms after the deviant sound).

The results of the aaaaa blocks fully replicated our earlier observations. During wakefulness, deviant sequences elicited a MMR with virtually the same three-component shape as in the first experiment (Fig. 33A). Again, an intermediate MMR effect was clearly present during wakefulness (108-156ms in temporal areas, $p < 0.05$) but vanished during N2 sleep, leaving only the early and late effects (early 84-124ms, $p < 0.05$; late 204-300ms, $p < 0.01$). Crucially, the aBaBa blocks revealed that this intermediate peak was entirely imputable to prediction error. During wakefulness, the deviant series aBaBB elicited a MMR characterized by a single deflection peaking around 150ms (100-200ms, $p = 0.001$), and essentially identical in latency and topography to the intermediate effect in aaaaa blocks (Fig. 33). This effect vanished during N2 sleep, such that the difference between aBaBa and aBaBB failed to reach significance. Thus, in a paradigm that separates predictive coding from sensory adaptation, sleep appears to selectively disrupt predictive coding.

II.4. Discussion

We investigated whether predictive coding, which is considered a fundamental property of the cortex, continues to operate during sleep. To this end, we tracked the responses of the sleeping brain when presented with auditory novelties at two distinct levels of complexity, either local (single-vowel change) or global (whole-sequence change), using a paradigm previously demonstrated to engage predictive-coding mechanisms (Wacongne et al. 2011). In spite of the continued presence of strong auditory potentials during sleep, the global effect (P300) disappeared abruptly, simultaneously with the loss of behavioral responsiveness during the descent to sleep, and was absent in both NREM and REM sleep. Local violations continued to elicit a distinctive response, but the peak of this local mismatch response, around 150ms, was sharply reduced. We then investigated which mechanism accounted for the residual mismatch effect that remained present during sleep. By dissociating predictive coding from sensory adaptation, we demonstrated that the mismatch peak that vanished during sleep was specifically associated with a prediction error signal. We now discuss how these results clarify whether and how sleep disrupts the processing of novel external stimuli.

II.4.1. Preserved auditory processing during sleep

Our results firmly establish that auditory stimuli (here single vowels) continue to enter the cortex and to be discriminated during sleep. Early perceptual responses of unchanged amplitude were detected in auditory cortices across all states of vigilance (Fig. 29 and 31). These early activations in primary auditory areas are in line with other studies demonstrating activations of auditory cortices during sleep (Peña et al. 1999; Portas et al. 2000; Edeline et al. 2001; Dang-Vu et al. 2011; Nir et al. 2013). Animal studies suggest that the burst firing mode of the thalamus during sleep, with its alternating on and off states, may be as effective as the tonic mode characteristic of wakefulness in relaying incoming sensory information to the cortex (Sherman 2001). However, changes in neuromodulatory control of thalamo-cortical excitability during sleep may attenuate sensory precision (Hobson and Friston 2012) which, in turn, would reduce the rate of evidence accumulation in sensory areas, thereby explaining the progressive increase in auditory latencies during sleep observed in the present study and in others (Bastuji et al. 1995; Nordby et al. 1996). Such an attenuation of the precision of sensory prediction errors may also explain the subsequent disruption in global and local effects (Hobson and Friston 2012).

II.4.2. Disrupted predictive coding during sleep

Prior research with inattentive subjects as well as coma and vegetative state patients has established that the global novelty response, associated with a P300 in EEG, depends on a conscious appraisal of the auditory sequence (Bekinschtein et al. 2009; Faugeras et al. 2012; Sitt et al. 2014). The present findings extend this result to sleep: the brain response to global novelty vanished abruptly with the loss of responsiveness during sleep. The all-or-none disappearance of the P300 occurred as early as stage 1 sleep, in which subjects were fluctuating between responsive and non-responsive states: responsive subjects showed a significant global effect in MEG and a P300 wave in EEG, while non-responsive subjects no longer did. This disappearance cannot be ascribed solely to a lack of motor preparation because, in both the present work (see Fig. 37) and in prior research (Wacongne et al. 2011), the global effect remained present with virtually identical topography, temporal profile and source localization, when awake subjects were merely told to attend to the stimuli without overtly responding.

The present results reinforce the notion that the global novelty response and, more generally, the P300 wave are phenomena that reflect conscious processes (Bekinschtein et al. 2009; Faugeras et al. 2012; Sitt et al. 2014; Sergent et al. 2005; Del Cul et al. 2007) and vanish suddenly under non-conscious conditions (Dehaene and Changeux 2011). Our results depict stage N1 sleep as a transition process from wakefulness to sleep, characterized by a mixture of conscious and non-conscious states inside the alpha-suppression periods. This hypothesis may explain previous results showing an attenuated P300 during N1 sleep (Bastuji et al. 1995): this result would arise from averaging over these two states, which indeed would have remained indistinguishable had we not used an explicit behavioral task.

Our findings are partially at odds with a set of previous studies using the oddball paradigm and which reported a small late posterior positivity during sleep around 300ms (Niiyama et al. 1994; Cote and Campbell 1999a; Cote et al. 2001; Takahara et al. 2006b) or 450ms (Bastuji et al. 1995; Sallinen et al. 1996) after deviant sounds. We note, however, that the oddball paradigm, unlike the present local-global paradigm, fails to dissociate the successive stages of novelty detection that are now known to possess very different properties in relation to consciousness (Bekinschtein et al. 2009; Wacongne et al. 2011; Faugeras et al. 2012; King et al. 2013a). Thus, we cannot exclude that these prior studies only observed the delayed response to a low-level (local) violation, rather than a genuine P300 response to high-level conscious predictive coding. Another possibility is that the stimuli used in these previous studies induced short periods of awakening. Here we purposely used low-intensity sounds (46 dB) and carefully monitored sleep stages to avoid this difficulty. Furthermore, we searched for novelty responses using a sensitive technique of MEG recording with 306 sensors followed by multivariate decoding, either trained directly on sleep data (Fig. 32c), or trained on a more extensive set of wake data from the same subject and then tested for generalization to sleep (Fig. 32a). Since

none of these efforts revealed a global novelty response, we can be confident that this response disappears during sleep in our paradigm.

The only exception was a small, early (<300ms) and transient global effect that remained elicited only by deviant sequences that had been previously heard consciously during wakefulness (Fig. 30b). This result suggests that, while the sleeping brain is unable to acquire a novel sequence during sleep, it remains able to detect deviations from a highly overlearned sequence repeatedly heard prior to sleep. The early time-window of this effect and the weak and transient generalization of decoding from pre-sleep to sleep (Fig. 32b) suggest that this response does not result from the sustained activation of the distributed “global workspace” underlying conscious responses to novelty (Bekinschtein et al. 2009; Dehaene and Changeux 2011), but may arise from a modular and automatic process localized to fronto-polar and peri-auditory areas (Fig. 4). Upon repetition during wakefulness, the sequence of 5 vowels (e.g. a,a,a,a,u) may become so highly familiar as to be stored as a unified auditory template similar to a word. The difference in brain response when a rare sequence is presented (e.g. a,a,a,a,a) may then reflect a sensory adaptation effect in units coding for this level (May and Tiitinen 2010). At any rate, the absence of any global effect with unfamiliar stimuli imply that such storage of frequent “words”, if present, is disrupted during sleep.

II.4.3. Disrupted mismatch response, but preserved adaptation during sleep

Previous research using the local-global paradigm indicated that, contrary to the global response, the local mismatch response can be preserved under conditions of distraction or unconsciousness (Bekinschtein et al. 2009; Faugeras et al. 2012). We therefore expected that this response might remain present during sleep. This prediction was only partially upheld, as a specific part of the mismatch response (MMR) elicited by local vowel deviants was also strongly affected by sleep. During wakefulness, the MMR was characterized by three steps of auditory processing: an early effect before 100ms, an intermediate effect peaking around 150ms (the MMN in EEG) and a late effect after 240ms. During sleep, the intermediate MMR effect/MMN was specifically reduced during N1 sleep and ultimately dropped to an undetectable level in N2 and REM sleep (Fig. 2A). Experiment 2 replicated these results (Fig. 33A) and demonstrated that the intermediate MMR component is specifically elicited by prediction errors during wakefulness, an effect that totally disappears during sleep (Fig. 33B). Thus, the MMR observed during wakefulness can be decomposed into (1) early and late components that result from adaptation mechanisms, and remain during sleep (2) a sharp intermediate peak that results from a prediction error and vanishes during sleep. This decomposition of the MMR is consistent with previous studies describing it as a complex phenomenon arising from multiple cortical areas with different qualitative properties (Giard et al. 1995; Garrido et al. 2009;

Pegado et al. 2010) and associating the intermediate MMR peak with predictive coding (Wacongne et al. 2011; Wacongne et al. 2012; Todorovic and de Lange 2012).

The formation of a prediction-error signal is thought to require a bidirectional transfer of information in both bottom-up and top-down directions, either locally across cortical layers (Wacongne et al. 2012) or across multiple areas of the cortical hierarchy (Friston 2005). Previous evidence suggests that the generators of the MMN extend beyond primary auditory cortices and involve a broad network including frontal and opercular cortices (Opitz et al. 2002; Näätänen et al. 2007; Garrido et al. 2009). Our source reconstructions confirm these localizations and suggest that they are specific to the intermediate time window of the MMR. The left inferior frontal pars opercularis area (Broca's area) location is also coherent with our use of vowel sequences, as this region is involved in the representation of structured language sequences (Petersson and Hagoort 2012).

Multivariate classifiers trained at the time of the intermediate mismatch peak were able to decode local deviants during wakefulness, but failed to generalize either to sleep (Fig. 32) or to other time periods (see the full temporal generalization matrix in supplementary Fig. 36). In past work, the temporal generalization of a classifier from one time point to another time has been shown to provide detailed information on the time course of brain activation (King and Dehaene 2014). King et al. (King et al. 2014) applied this method to the local-global paradigm and showed, exactly as in the present work, that the intermediate MMR was focal in time and did not generalize to the early and late time periods.

In spite of the disruption of markers of predictive coding during both NREM and REM sleep, a slight recovery of the progressive ramping-up of brain responses was observed during REM sleep (Fig.2). This effect has been previously associated with an expectation of the fifth sound in the sequence (Chennu et al. 2013), an interpretation which would appear to contradict the observed disruption of predictions during sleep. However, this ramping-up can also be interpreted as a passive summation of the activation evoked by each successive vowel, without involving top-down expectations. Further research will be needed to disentangle these two interpretations, and to clarify which aspects of the processing of external auditory stimuli may recover during REM sleep.

Unlike predictive coding, adaptation is considered a basic property of bottom-up sensory transmission localized to primary auditory cortex (Ulanovsky et al. 2003; Farley et al. 2010; Fishman and Steinschneider 2012). We indeed showed that the early MMR effect localizes almost exclusively to auditory areas during both wakefulness and sleep (Fig.31). The late effect was also localized to auditory cortices during sleep, but activations propagated more broadly into the cortex during wakefulness (Fig.31). The similarities of mechanisms between the early and late MMR are strengthened by the successful temporal generalization from one effect to the other in both states of

vigilance (Fig. S3). Decoding analyses also confirmed the similarities of these effects between wakefulness and sleep, as decoding generalized successfully from one state to the other (Fig.32A and S30).

The hypothesis of preserved sensory adaptation during sleep was supported by a recent electrophysiological study in rats (Nir et al. 2013). Our results confirm this possibility in humans. They further show that the recovery from adaptation for deviant sounds is particularly large for stimuli that have never been heard prior to sleep (Fig. 30), compared to sounds that were extensively presented prior to sleep and while falling asleep. Only the new local deviants elicited activations spreading into the precuneus (Fig. 4). By reaching this region putatively involved in consciousness and self-awareness (Cavanna and Trimble 2006), novel deviant tones may bring the brain closer to the awakening threshold. The proposed preservation of stimulus-specific adaptation during sleep may therefore explain why the presentation of novel sounds may lead to awakening, while familiar sounds such as a clock ticking do not.

Overall, our results indicate that the cortex continues to process auditory stimuli during sleep, and to adapt to them, but that two components of brain activity related to hierarchical predictive coding vanish during sleep: the global effect and the intermediate peak of the local mismatch response. Future research should test whether these findings can be generalized to other prediction paradigms that are also thought to depend on a bidirectional bottom-up and top-down exchange of cortical signals (Friston 2005). This hypothesis would be compatible with a vast literature that indicates a breakdown of cortical communication and temporal integration during sleep (Massimini et al. 2005; Horowitz et al. 2009; Tagliazucchi et al. 2013b).

II.5. Materials and Methods

II.5.1. Experiment 1

II.5.1.1. Auditory stimuli and block design

Four pairs of natural French vowels were recorded. Each pair was composed of one vowel of a male pitch and the other of a female pitch, chosen to be distant in the vocalic triangle (a-y; i-o; u-ë; e-õ). They were normalized for intensity, limited to 100-ms-duration with 10-ms rise and 10-ms fall times (Audacity 1.3 beta, Unicode Software) and presented under software control (Psychtoolbox

software PTB-3, Matlab -R2010a) via a loudspeaker in the MEG room, at a low intensity of 46 dB. Trials were composed of sequences of 5 vowels with 150ms stimulus onset asynchrony and were separated by silent gaps of variable duration (700 to 1000ms inter-trial interval, 50ms steps). Each block of 100 consecutive sequences comprised two types of sequences: the local standard sequences with five identical vowels (aaaaa) and the local deviant sequences with the fifth vowel different from the first four ones (aaaaB, a and B denoting the vowels of one pair). The global regularity was established by first repeating one of the sequences (global standard, either aaaaa or aaaaB) 10 times during a habituation block, then on 80% of the remaining 90 trials. The other sequence (global deviant, respectively aaaaB or aaaaa) was presented on the remaining 20% of trials. Sequences were presented in a pseudo-random order with the constraint that two global deviants could not appear in succession nor be separated by more than 7 global standards. The local mismatch effect was defined as the difference between local deviants and local standards (i.e. aaaaB minus aaaaa), and the global effect as the difference between global standards and global deviants (i.e. rare minus frequent sequences).

II.3.1.2. Procedure

Subjects were tested before sleep (Wake_{PRE}), during (Sleep) and after a morning nap (Wake_{POST}). The experiment started with the presentation during the Wake_{PRE} session of a first set of stimuli (stimulus set 1) comprising 2 aaaaa and 2 aaaaB blocks. Each block type was presented twice in order to counterbalance the vowels (one pair was used for aaaaa blocks, the other for aaaaB blocks). Subjects were asked to respond to global deviant sequences by pressing a button. Once these blocks were complete, they continued to hear the stimulus set 1 (blocks continued to alternate every 2 min 35 seconds without gaps), and were still asked to give a motor response to global deviant stimuli, but they were told that at some point they would probably fall asleep and stop responding. Visual EEG and MEG on-line monitoring allowed tracking their descent into stage N1 and then stage N2 sleep. During stage N2, alongside stimulus set 1 (N2-Sleep_{OLD} blocks), a novel set of stimuli with new vowels was introduced (stimulus set 2; 2 aaaaa and 2 aaaaB blocks; N2-Sleep_{NEW} blocks). The time necessary to complete the 8 N2-Sleep blocks (Sleep_{OLD} + Sleep_{NEW}) was about 25 min. If subjects woke up during N2-Sleep_{NEW} blocks, stimuli were immediately changed back to stimulus set 1. Any such interrupted blocks were presented again in full once subjects returned to stage N2 sleep. A subset of 11 subjects reached REM sleep and was presented with both sets of stimulus 1 and 2. After sleep during the Wake_{POST} session, subjects were presented with stimulus set 2 and again asked to give a motor respond to global deviants. Subjects were asked to keep their eyes closed throughout the experiment, even when awake. The assignment of response hands and of vowels was randomized between subjects.

II.3.1.3. Subjects

31 healthy right-handed subjects between 18 and 35 years old were recruited on a voluntary basis after giving written informed consent. The study was approved by the local Ethical Committee. Subjects had no neurological, auditory, psychiatric or sleep disorders. They did not receive any psychotropic treatment and had no excessive consumption of caffeine or alcohol, or other drug use. They were selected to be easily prone to naps, on the basis on a short questionnaire evaluating their frequency of napping (≥ 1 /week) and their ability to nap in noisy or uncomfortable conditions (train, plane,...). Addition selection criteria included sleeping in the supine position on the back and being non-snorers. They were asked to avoid drinking any exciting drinks (coffee, tea...) or alcohol 24h before the experiment. All of them complied with the sleep restriction. 23 subjects reached sleep stage 2 and slept long enough to be presented with some stimuli. Of these, only subjects with a clearly visible auditory evoked potential were kept. In N2-sleep, 19 subjects met this criterion (12 females, 7 males). Those subjects were kept for analysis during wakefulness for direct comparisons with N2 Sleep. For lack of sufficient data, one subject was removed for N2-Sleep_{NEW} and another for N2-Sleep_{OLD} condition. Sleep_{OLD} and Sleep_{NEW} analysis were thus conducted on 18 subjects each. For REM sleep, only 9 subjects (out of the 11 who reached this stage) had enough data to meet the criterion and to be included. Analyses were not performed during deep sleep (N3 sleep) as only eight subjects reached this stage during the nap. During N1 sleep, subject inclusion was also based on the compliance with the motor task (some subjects were excluded for reporting, during debriefing, that they purposely stopped responding at some point in order to be able to fall asleep). 13 subjects were thus kept for analysis.

II.3.1.4. Simultaneous M/EEG Recording

EEG and MEG signals were recorded simultaneously with the Elekta Neuromag system (Elekta Neuromag Oy - 204 planar gradiometers and 102 magnetometers - in supine position) and its built-in EEG system (60 channels). Electrocardiogram (ECG), electro-oculogram (EOG) (horizontal and vertical) and chin electromyogram (EMG) were recorded as auxiliary bipolar channels. EEG was referenced to the right mastoid. EEG, EOG and EMG signals were used to monitor sleep stages on-line. MEG, EEG, and auxiliary channels were low-pass filtered at 330 Hz, high-pass filtered at 0.1 Hz, and sampled at 1 KHz. The head position in the MEG sensor array was acquired continuously during each block thanks to four head-position indicator coils attached to the scalp. These coils and EEG electrodes positions were previously digitized with respect to three anatomical landmarks (nasion and preauricular points) with a 3D digitizer (Polhemus Isotrak system).

II.3.1.5. Sleep Analysis

The sleep stages were re-scored off-line by two independent sleep experts (M.S. and M.E.) according to the new AASM guidelines – 2007 (FASST software, <http://www.montefiore.ulg.ac.be/~phillips/FASST.html>). Inter-scorer agreement was high (96%). Scorers jointly agreed on the remaining recordings, and any ambiguous period or transition between two stages was removed from analysis. For N1 sleep analysis, only periods free of alpha waves were kept. Indeed, alpha waves are present at the initiation of N1 sleep before their complete suppression, as described by the Hori et al. classification (Hori et al. 1994). These alpha waves are ambiguous transition periods, indistinguishable from micro-arousals or relaxed wakefulness with eyes closed. Note that during wakefulness in the present study, alpha waves were present in virtually all epochs, as subjects were told to close their eyes. As we wanted to avoid any ambiguity and analyze only trials occurring within a robust N1 sleep stage, we kept for N1 analysis only epochs without alpha waves corresponding to Hori stages H4 to H8. In N2 sleep, K-complexes and micro-arousals were manually detected and excluded from analysis (percentages of rejected trials for K-complexes: mean = 5.0%, median = 4.3%, for micro-arousals: mean=8.2%, median=6.8%). In REM sleep, micro-arousals, as defined by an abrupt increase of EEG frequency with a concurrent increase of muscle tone (AASM 2007), were also removed (mean=4.3%, median=3.7%). An example of sleep scoring is shown in Fig. S5.

II.3.1.6. Preprocessing and data analysis

Data were preprocessed using MaxFilter Software (Elekta Neuromag) for signal space separation correction, continuous head movement compensation and bad channels correction (detected visually from the raw signal). Principal components analysis was used to remove cardiac artifacts. The continuous signal was then down-sampled to 250Hz and filtered between 0.3 and 30Hz (MNE software (Gramfort et al. 2014)). Using Fieldtrip software (Oostenveld et al. 2011) (<http://www.ru.nl/neuroimaging/fieldtrip>) trials were epoched from 200ms before to 1450ms after the onset of the first sound, after correction for the stimulus-trigger time delay. EEG data were re-referenced to an average reference after bad channels interpolation. Outlier trials were automatically rejected when deviating from more than twice the average deviation from the mean (<http://audition.ens.fr/adc/NoiseTools/>). The remaining trials were averaged per condition and per subject, and baseline corrected using the first 200ms of the epoch.

Statistical analyses were performed with cluster permutation tests corrected for multiple comparisons over time and sensor space (Fieldtrip software; Monte-Carlo method, 1000 permutations, alpha level for the two-side permutation t-tests = 0.025, p value < 0.05 for significant clusters). Based

on prior results (Bekinschtein et al. 2009; Wacongne et al. 2011), a-prior search windows were defined between 48 and 498ms for the local mismatch effect and between 48 and 700ms for the global effect for both EEG and MEG data. Our MEG system has three different types of sensors orthogonally oriented in space (two planar gradiometers and one axial magnetometer) thus combining the focal sensitivity of gradiometers with the deep-source sensitivity of magnetometers (Parkkonen 2010). Analyses were performed separately on each type of sensor for local and global effects. As shown in fig. S1 and S2, local and global effects were clearly visible in all types of sensors. However, as previously observed (Wacongne et al. 2011), gradiometers oriented along the dy axis (gradiometers type 2) showed the highest statistical sensitivity. For simplicity, we therefore report topographies, time series and statistical analyses conducted on those MEG sensors.

Early auditory responses across states of vigilance were further analyzed on a set of four gradiometers lying closest to the left auditory cortex. Analyses on the slope of evoked responses along sequences were performed by computing the linear regression between the first and the fifth sound and comparing slopes between stages of vigilance. As the number of subjects was different between sleep stages, we tested for differences using paired Wilcoxon signed-rank tests, using only those subjects for whom data was available in the two vigilance states tested.

II.3.1.7. Source Reconstructions

Anatomical T1-weighted MRIs were acquired for each subject (3-T Siemens). Cortex segmentation (gray-white matter boundary) was done with Freesurfer software (<http://surfer.nmr.mgh.harvard.edu/>). Estimation of current source density was performed with BrainStorm software (Tadel et al. 2011) (<http://neuroimage.usc.edu/brainstorm/>). After cortical and scalp reconstructions, anatomy and MEG signal were co-registered using head-position indicators and EEG electrodes position on the scalp previously digitized. The forward problem was computed using an overlapping spheres model. Noise covariance was estimated from empty-room MEG recordings acquired before each subject's recording. Individual sources were computed with weighted minimum-norm method and dSPM option (depth weighting factor of 0.8, loosing factor of 0.2 for dipole orientation), separately for local and global effects. They were then projected on a standard anatomical template to perform averages across subjects. Absolute values of the time series in regions of interest are shown.

II.3.1.8. Multivariate decoding

Multivariate pattern classifiers were trained as previously described (King et al. 2013a). Separate classifiers were trained to discriminate local standard trials from local deviant trials, and

global standard trials from global deviant trials. For each analysis, the data consisted in a matrix composed of n trials and f features, where each feature correspond to the amplitude of the MEG signal recorded in a given sensor at a given time point. Briefly, the data was first normalized independently of the trial classes: for each feature separately, the mean across trial was subtracted and the data was divided by the standard deviation across trials. A univariate feature selection was then applied to restrict the subsequent steps to the 30% most discriminative features. A linear support vector machine (Chang and Lin 2011) was then fitted to the resulting data, in order to find the hyperplane that best separated standard and deviant trials. Following King et al.'s study (2013a), the penalization parameter remained fixed to $C=1$, and a sample weight method was applied to limit the effect of class imbalance. Finally a logistic function was fitted on the projection of the data onto the hyperplane, in order to provide, for each trial, an estimate of the probability that it belonged to each class. All of the above steps (normalization, feature selection, SVM, logistic fit) were performed within an eight-fold cross-validation scheme. In each fold, the computation were fitted onto $7/8^{\text{th}}$ of the trials (training set) and applied to the remaining $1/8^{\text{th}}$ of the trials (independent test set). Cross validation was stratified in order to keep the same proportion of each trial type in each fold.

Decoding performance was summarized with an empirical receiver operative curve (ROC) analysis and its area under the curve (AUC). AUCs were computed for each subject and grand-averaged across subjects. Significance was tested within subjects using Mann–Whitney U tests across trials. Correspondingly, across-subjects statistics were computed using Wilcoxon Signed Rank Tests on the mean predicted probability of the true trial class.

Using the Wake_{PRE} data in [-150,750] ms time window, two classifiers were trained separately for the local effect (separating local deviants from local standards) and for the global effect (separating local deviants from local standards). These classifiers were subsequently tested on their ability to generalize to N2-Sleep and to $\text{Wake}_{\text{POST}}$. To maximize the detection of novelty effects during sleep, two additional classifiers were trained only on N2-sleep data.

II.5.2. Experiment 2

The design was identical to experiment 1 with the following exceptions (see Fig. 6). Two blocks of 100 sequences were presented: aaaa blocks identical to the first experiment, and a second type of block in which new vowel pairs were used to build two standard sequences of 5 alternating vowels (aBaBa and BaBaB) and 2 deviant sequences including a final repetition (aBaBB and BaBaa). Sequences were randomly presented with an equal frequency (25% each). In this manner, the two vowels had the same absolute frequency, but the transition probabilities differed, as vowel alternation was much more probable ($7/8$) than vowel repetition ($1/8$).

11 healthy right-handed subjects between 18 and 35 years old, different from the first experiment, were recruited. Because the focus was on the MMR, subjects were not asked to perform any explicit behavioral task. All subjects fell asleep and were included in the analysis. Statistical cluster permutation tests were computed between 0 and 300ms after the fifth sound of series, a search window defined from the results of the first experiment in order to focus on the three MMR components.

II.6. Supplementary Materials

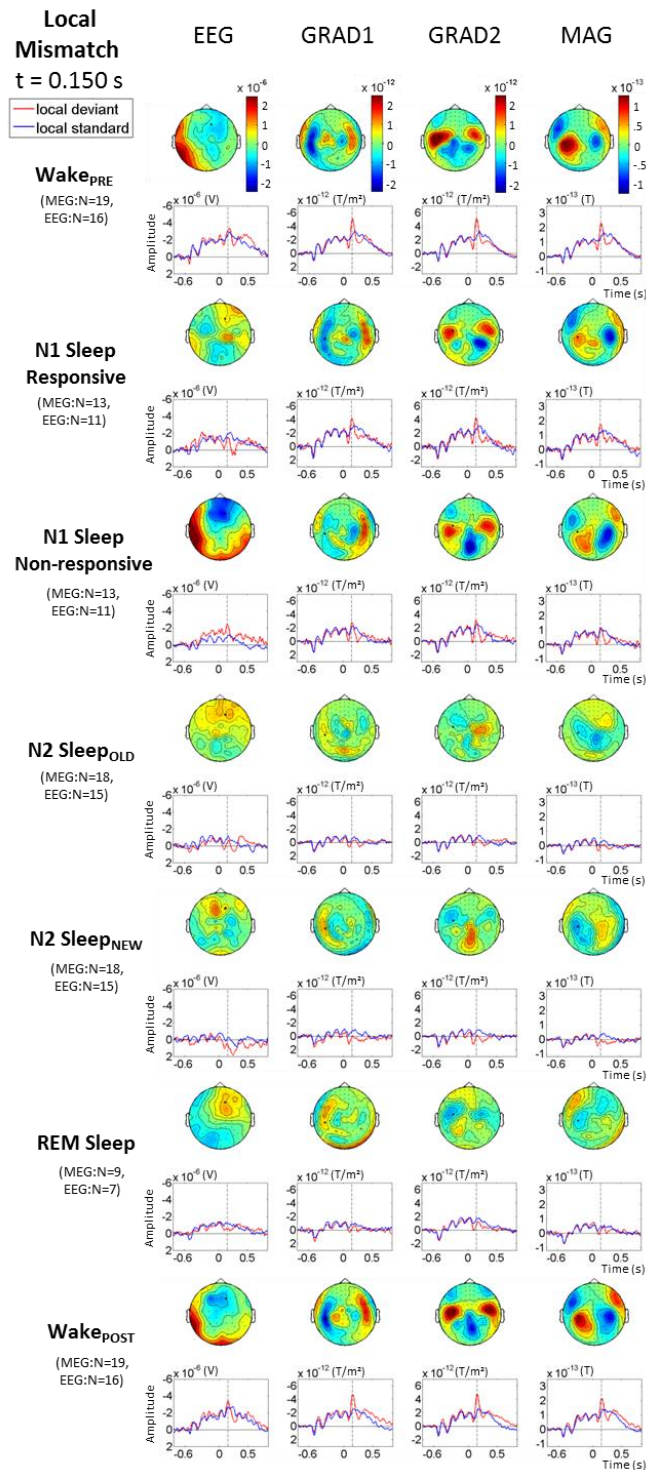


Figure 34. Local Mismatch effect through the different states of vigilance.

Grand-averages for all sensor types are represented. From left to right: EEG and the 3 MEG sensor types, with planar gradiometer 1 (GRAD1) and 2 (GRAD2) and magnetometers (MAG). The number of subjects (N) in each condition is specified. Topographies at 150ms after the fifth sound are represented (vertical dotted line).

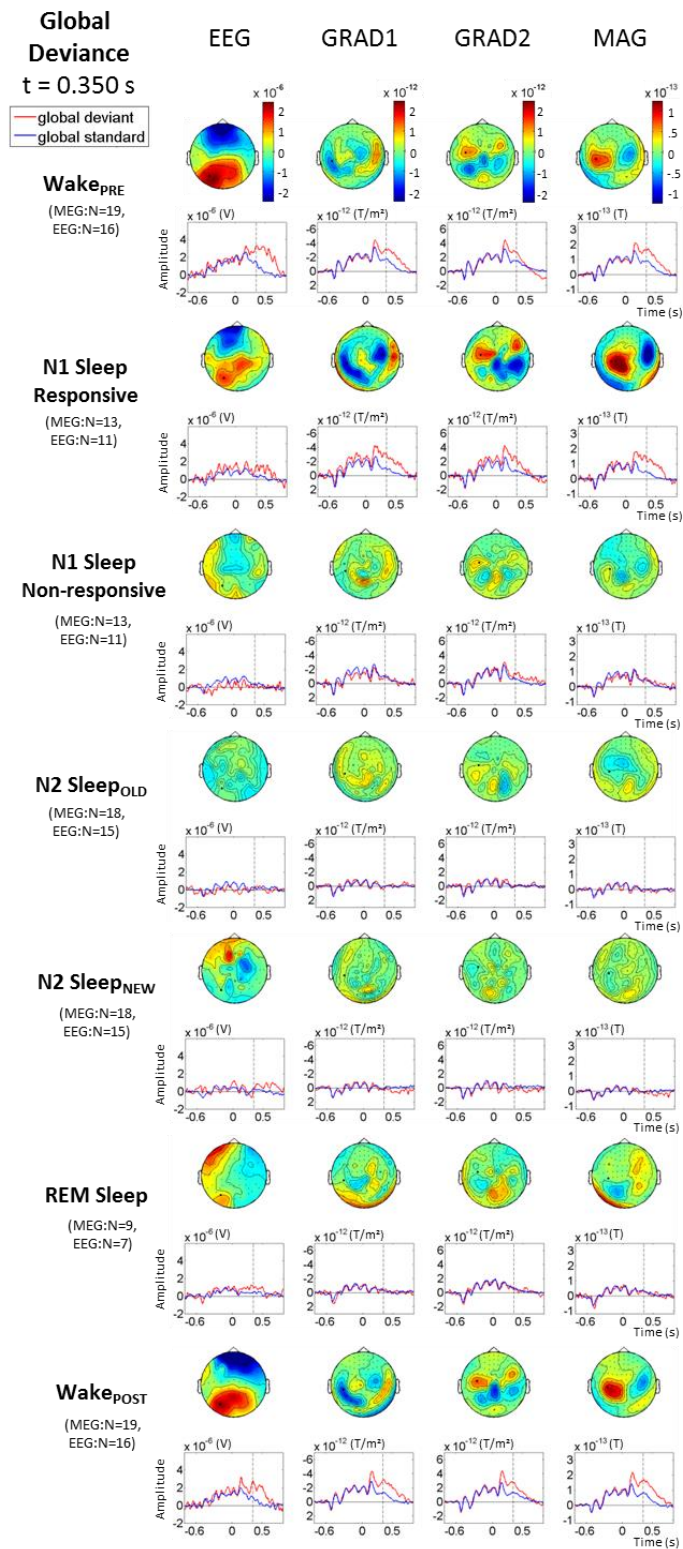


Figure 35 Global deviance effect through the different states of vigilance.

Same format as Fig. S1. Topographies at 350ms after the fifth sound are represented (vertical dotted line).

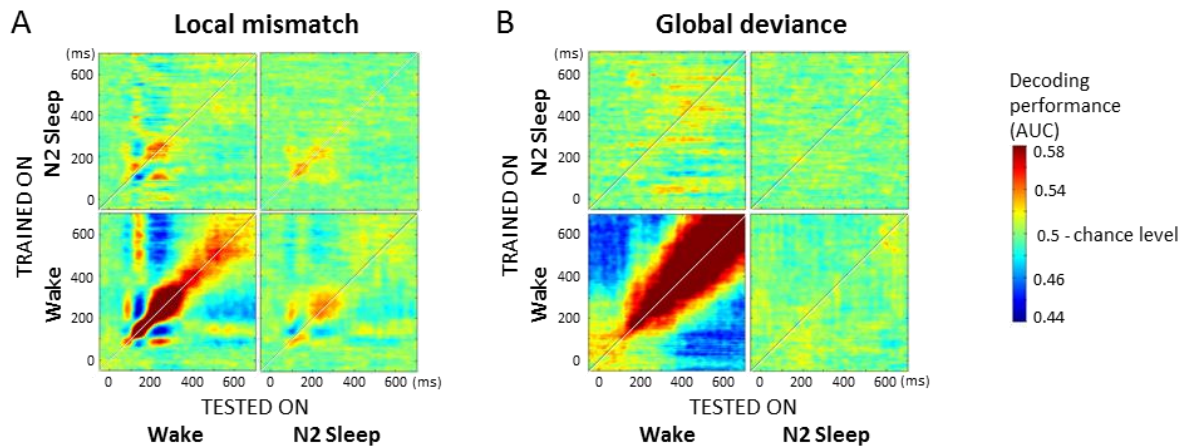


Figure 36. Decoding generalization across time and states of vigilance.

Each classifier trained at a given time point and data set was tested on data from every time point and every data set. The trained dataset are represented on the vertical axis and the tested dataset on the horizontal one. The color scale represents the area under the curve (AUC). **A. Local mismatch.** Each of the early and late effects generalizes across the waking state and N2 sleep, and they are mutually generalizable in each state of vigilance. Off-diagonal positive generalization across wakefulness and sleep during the early time window of the local mismatch indicates that the early MMR is slightly delayed during N2 sleep compared to wakefulness. The intermediate mismatch response is only decoded during wakefulness and generalizes beyond 400ms. **B. Global deviance.** A global novelty response is only decodable in the waking state, from 150ms, with an increasingly sustained response over time.

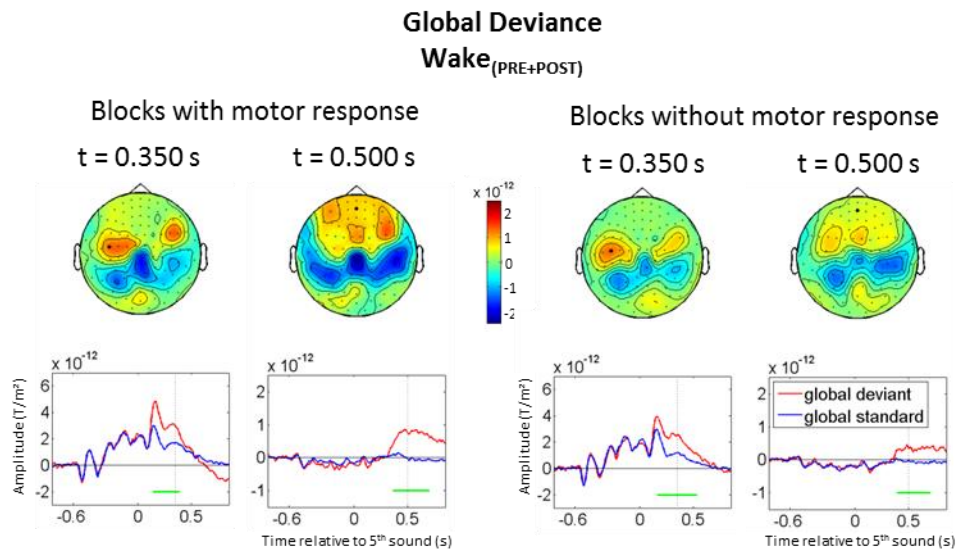


Figure 37. Global effect during wakefulness in blocks with and without motor response after global deviants.

The global effect is characterized by activations starting in temporal regions and spreading to anterior areas. The global effect is virtually the same in case of motor responses after global deviants (left) or if subjects are told to attend to stimuli without giving motor responses (right). Topographies are shown at 350 and 500ms with ERF time series of one left temporal and one anterior sensor and corresponding significant activations (horizontal green lines, $p < 0.05$).

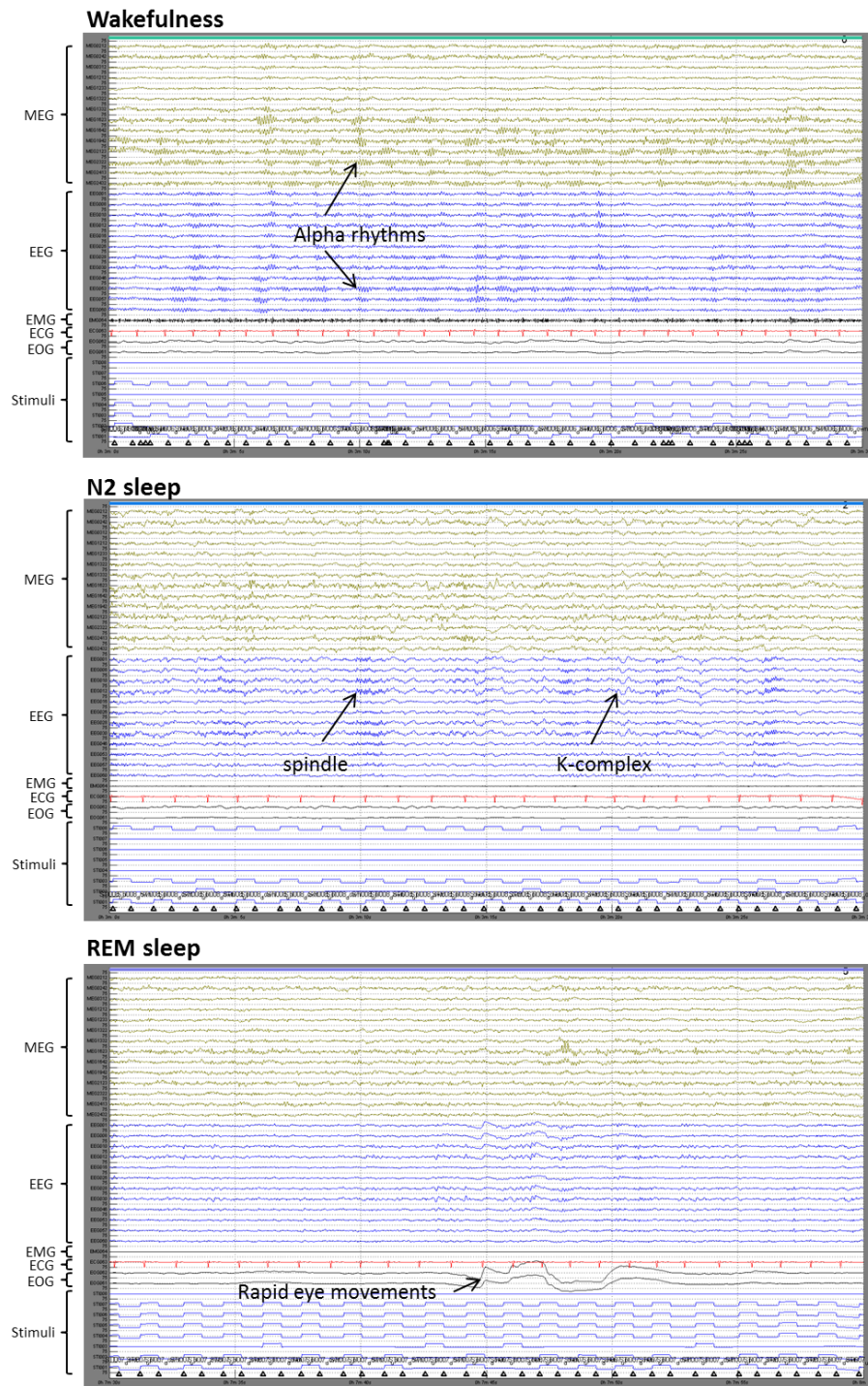


Figure 38. Example of polysomnography.

30s epochs of wakefulness, N2 sleep and REM sleep for one subject are shown. On each epoch MEG, EEG, EMG, ECG and EOG signals are displayed, along with triggers corresponding to the sequences of stimuli. Wakefulness (eyes closed) is characterized by rapid EEG-MEG activities with posterior alpha rhythms and the presence of muscle tone. In N2 sleep the EEG-MEG activities are slower (theta rhythms), with sleep spindles and K-complexes. The muscle tone is reduced. In REM sleep the EEG-MEG activities are increased with theta and alpha rhythms. Rapid eye movements are presents and the muscle tone is abolished.

Amplitude (e-12T)	Wake_{PRE} (N=19) -1.05	N1 Sleep (N=19) -1.20	N2 Sleep (N=19) -1.05	REM Sleep (N=9) -0.88	Wake_{POST} (N=19) -1.26
Wake_{PRE} -1.05		p = 0.26 (N=19)	p = 0.63 (N=19)	p = 0.65 (N=9)	p = 0.04 * (N=19)
N1 Sleep -1.20	p = 0.26 (N=19)		p = 0.12 (N=19)	p = 0.82 (N=9)	p = 0.42 (N=19)
N2 Sleep -1.05	p = 0.63 (N=19)	p = 0.12 (N=19)		p = 0.56 (N=6)	p = 0.13 (N=19)
REM Sleep -0.88	p = 0.65 (N=9)	p = 0.82 (N=9)	p = 0.56 (N=6)		p = 0.20 (N=8)
Wake_{POST} -1.26	p = 0.04 * (N=19)	p = 0.42 (N=19)	p = 0.13 (N=19)	p = 0.20 (N=8)	

Latency (ms)	Wake_{PRE} (N=19) 70.7	N1 Sleep (N=19) -81.5	N2 Sleep (N=19) 100.4	REM Sleep (N=9) 94.2	Wake_{POST} (N=19) 76
Wake_{PRE} 70.7		p = 0.036 * (N=19)	p = 0.001 ** (N=19)	p = 0.51 (N=9)	p = 0.56 (N=19)
N1 Sleep 81.5	p = 0.036 * (N=19)		p = 0.002 ** (N=19)	p = 0.17 (N=9)	p = 0.26 (N=19)
N2 Sleep 100.4	p = 0.001 ** (N=19)	p = 0.002 ** (N=19)		p = 0.88 (N=6)	p = 0.001 ** (N=19)
REM Sleep 94.2	p = 0.51 (N=9)	p = 0.17 (N=9)	p = 0.88 (N=6)		p = 0.16 (N=8)
Wake_{POST} 76	p = 0.56 (N=19)	p = 0.26 (N=19)	p = 0.001 ** (N=19)	p = 0.16 (N=8)	

Table 1. Amplitudes and latencies of the 1st evoked peak after sequence onset.

Mean amplitudes and latencies for each state are reported in the top line and the first column. Statistical differences between states of vigilance are reported (paired Wilcoxon sign rank test). For greater readability, the same values are repeated above and below the diagonal. The variable number of subjects (N) reflects the fact that some subjects did not reach a particular sleep stage. N1 Sleep includes both N1-responsive and N1-non-responsive states, and N2 Sleep includes both SleepOLD and SleepNEW, as their respective latencies and amplitudes were not statistically different. *p<0.05, **p<0.01.

Amplitude (e-12T)	Wake _{PRE} (N=19) 1.88	N1 responsive (N=13) 1.86	N1 non- responsive (N=13) 1.17	N2 Sleep (N=19) -1.05	REM Sleep (N=9) -0.88	Wake _{POST} (N=19) -1.26
Wake _{PRE} 1.88		p = 0.89 (N=13)	p = 0.02 * (N=13)	p = 3e-04 ** (N=19)	p = 0.01 * (N=9)	p = 8e-04 ** (N=19)
N1 responsive 1.86	p = 0.89 (N=13)		p = 0.03 * (N=13)	p = 0.01 ** (N=11)	p = 0.25 (N=4)	p = 0.23 (N=13)
N1 non-responsive 1.17	p = 0.02 * (N=13)	p = 0.03 * (N=13)		p = 0.06 (N=11)	p = 0.25 (N=4)	p = 0.97 (N=13)
N2 Sleep -1.05	p = 3e-04 ** (N=19)	p = 0.01 ** (N=11)	p = 0.06 (N=11)		p = 1 (N=6)	p = 0.04 * (N=19)
REM Sleep -0.88	p = 0.01 * (N=9)	p = 0.25 (N=4)	p = 0.25 (N=4)	p = 1 (N=6)		p = 0.25 (N=8)
Wake _{POST} -1.26	p = 8e-04 ** (N=19)	p = 0.23 (N=13)	p = 0.97 (N=13)	p = 0.04 * (N=19)	p = 0.25 (N=8)	

Latency (ms)	Wake _{PRE} (N=19) 157.7	N1 responsive (N=13) 169.2	N1 non- responsive (N=13) 182.8	N2 Sleep (N=19) 179.8	REM Sleep (N=9) 183.6	Wake _{POST} (N=19) 158.7
Wake _{PRE} 157.7		p = 0.37 (N=13)	p = 0.21 (N=13)	p = 0.02 * (N=19)	p = 0.71 (N=9)	p = 0.81 (N=19)
N1 responsive 169.2	p = 0.37 (N=13)		p = 0.46 (N=13)	p = 0.43 (N=11)	p = 0.25 (N=4)	p = 0.004 ** (N=13)
N1 non-responsive 182.8	p = 0.21 (N=13)	p = 0.46 (N=13)		p = 0.75 (N=11)	p = 1 (N=4)	p = 0.04 * (N=13)
N2 Sleep 179.8	p = 0.02 * (N=19)	p = 0.43 (N=11)	p = 0.75 (N=11)		p = 0.44 (N=6)	p = 0.007 ** (N=19)
REM Sleep 183.6	p = 0.71 (N=9)	p = 0.25 (N=4)	p = 1 (N=4)	p = 0.44 (N=6)		p = 0.57 (N=8)
Wake _{POST} 158.7	p = 0.81 (N=19)	p = 0.004 ** (N=13)	p = 0.04 * (N=13)	p = 0.007 ** (N=19)	p = 0.57 (N=8)	

Table 2 Amplitudes and latencies of the 2nd evoked peak after sequence onset.

Same format as table S1, but N1 responsive and N1 non-responsive states are separated. *p<0.05, **p<0.01.

Slope (e-14T)	Wake _{PRE} (N=19) 1.32	N1 responsive (N=13) 1.63	N1 non- responsive (N=13) 1.39	N2 Sleep (N=19) 0.70	REM Sleep (N=9) 1.04	Wake _{POST} (N=19) 1.37
Wake _{PRE} 1.32		p = 0.24 (N=13)	p = 1 (N=13)	p = 0.001 ** (N=19)	p = 0.43 (N=9)	p = 0.69 (N=19)
N1 responsive 1.63	p = 0.24 (N=13)		p = 0.50 (N=13)	p = 0.005 ** (N=11)	p = 0.13 (N=4)	p = 0.27 (N=13)
N1 non-responsive 1.39	p = 1 (N=13)	p = 0.50 (N=13)		p = 0.005 ** (N=11)	p = 0.38 (N=4)	p = 0.73 (N=13)
N2 Sleep 0.70	p = 0.001 ** (N=19)	p = 0.005 ** (N=11)	p = 0.005 ** (N=11)		p = 0.03* (N=6)	p = 8e-04 ** (N=19)
REM Sleep 1.04	p = 0.43 (N=9)	p = 0.13 (N=4)	p = 0.38 (N=4)	p = 0.03* (N=6)		p = 0.008 ** (N=8)
Wake _{POST} 1.37	p = 0.69 (N=19)	p = 0.27 (N=13)	p = 0.73 (N=13)	p = 8e-04 ** (N=19)	p = 0.008 ** (N=8)	

Table 3. Slopes of the progressive ramping-up of evoked responses from first to fifth sound (-600 to 0ms).

Same format as table S2. *p<0.05, **p<0.01.

II.7. Acknowledgments

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III. DETECTION OF ARITHMETIC VIOLATIONS DURING SLEEP

III.1. Abstract

We tested the capacity of the sleeping brain to develop predictions of future auditory stimuli for over-learned semantic knowledge stored in long-term memory. We presented sleeping subjects with simple arithmetic facts such as “two plus two is nine” and recorded brain responses to correct or incorrect results in electro and magneto-encephalography. Arithmetic violations, compared to correct results, still elicited small but significant responses during NREM and REM sleep. A partial N400 effect was preserved, with activations of auditory and semantic networks suggesting the preservation of physical stimulus properties and semantic incongruity detection. We suggest that, although sleep disrupts explicit arithmetic computations, there is a preservation of error signals for arithmetic facts stored in long-term memory.

III.2. Introduction

During sleep, environmental stimulations are not perceived consciously. Sensory stimuli integration appears to be disrupted along with the profound modifications in brain activities during sleep, as slow rhythms, decreased long-distant connectivity across brain regions (Spoormaker et al. 2012; Boly et al. 2012; Tagliazucchi et al. 2013b) and hypoactivity of associative areas such as the prefrontal cortex (Braun et al. 1997). However, growing evidence suggests that sensory stimuli still enter primary cortices during sleep (Portas et al. 2000; Strauss et al. 2015) and may be processed through multiple sensory-motor or cognitive domains. Among others, sensory adaptation (Strauss et al. 2015), reaction to forename (Perrin et al. 1999), semantic processing (Brualla et al. 1998; Ibáñez et al. 2006; Daltrozzo et al. 2012; Kouider et al. 2014), task-relevant motor preparation (Kouider et al. 2014), and even implicit learning as manifested by classical conditioning (Arzi et al. 2012) have been reported during sleep.

These examples suggest that the sleeping brain may still process external information, but mostly in the context of implicit, automatic and over-learned knowledge. In a previous study, we demonstrated that auditory violations of temporal regularities that were arbitrary and recently acquired

were not detected during sleep (Strauss et al. 2015). In the present work, we decided to investigate the sleeping brain's ability to detect violations of familiar auditory stimuli. We aimed to assess whether novelty detection could still occur for highly over-learned knowledge, i.e. knowledge of elementary arithmetic facts.

Numbers are robustly represented in the brain, in adult humans but also in infants and in non-human species (Dehaene et al. 2004b; Feigenson et al. 2004). Previous studies demonstrated that parts of the networks involved in arithmetic can be activated non-consciously. Digits or number words masked below the threshold for conscious perception biased a number-comparison task and induced activations in bilateral intra parietal sulci (IPS) (Naccache and Dehaene 2001). Evidence for unconscious semantic processing was obtained in subliminal priming paradigms (Greenwald et al. 1996; Luck et al. 1996; Dehaene et al. 1998b; Kiefer and Spitzer 2000), in fMRI and EEG in vegetative state patients (Coleman et al. 2007; Rohaut et al. 2015) and during sleep (Brualla et al. 1998; Ibáñez et al. 2006; Daltrozzo et al. 2012; Kouider et al. 2014). However, only a few studies have for now assessed directly the question of possible non-conscious arithmetic processing. Lefevre and collaborators (Lefevre et al. 1988) first showed that simple arithmetic facts were automatically processed independently of the task. When presenting a pair of single digits (e.g., 6+1) followed by a probe (e.g., 7), with the task to verify the presence of the probe digit in the previously presented pair, reaction times were increased when the probe digit was the sum of the pair. Using visual masked priming paradigms (Galfano et al. 2004; Rusconi et al. 2006; García-Orza et al. 2009; Ric and Muller 2012) or continuous flash suppression (Sklar et al. 2012), subliminal studies also suggested that arithmetic rules may be partially computed non-consciously. To the best of our knowledge, however, arithmetic was never tested during sleep.

In order to assess such arithmetic processing during sleep, in the absence of overt behavior, we needed to look for their electrophysiological correlates. In EEG in conscious condition, the presentation of incorrect arithmetic facts (e.g., $2+2=9$) in comparison to correct ones (e.g., $2+2=4$) elicit a succession of N400 and P600 waves, very similar to the ones elicited after semantic violations (Niedeggen et al. 1999; Niedeggen et al. 1999). The N400 was first described in response to words that violate the semantic context of the sentence, characterized by an EEG central negativity elicited around 400 ms after the incongruent word (Kutas and Hillyard 1980) (e.g. "He took a paper and pencil to... fly"). After both semantic and arithmetic violations, this N400 is followed by a late centro-posterior positivity, named P600, believed to be related to cognitive control mechanisms and rule violation detection (Niedeggen et al. 1999; Núñez-Peña and Honrubia-Serrano 2004; Szűcs and Soltész 2010; Brouwer and Hoeks 2013; Sassenhagen et al. 2014). It has often been compared to the P300, considering that it follows the same spatial dynamic, increases in amplitude with violation of expectancy, and is time-locked to the motor response (as the P300 is) while the N400 is stimulus-

locked (Szűcs and Soltész 2010; Sassenhagen et al. 2014; Sassenhagen and Bornkessel-Schlesewsky 2015).

The semantic N400 has already been reported in various non-conscious conditions, in subliminal paradigms (Holcomb 1993; Luck et al. 1996; Kiefer and Spitzer 2000; Kiefer 2002; Kiefer and Brendel 2006; van Gaal et al. 2014), in vegetative state (Rohaut et al. 2015), and even during sleep (Brualla et al. 1998; Ibáñez et al. 2006; Daltrozzo et al. 2012). At the contrary, the P600 failed to be recorded in those subliminal conditions (Batterink and Neville 2013; van Gaal et al. 2014), suggesting that it reflects conscious processing. Evidence for a non-conscious arithmetic N400 is much less abundant (Galfano et al. 2004), and no P600 was reported.

We then tested the sleeping brain's abilities to anticipate arithmetic results and evaluate their correctness in a verification paradigm known to elicit N400-P600 effects. We recorded simultaneously EEG and magnetoencephalographic (MEG) responses to auditory presented correct or incorrect arithmetic facts, looking for N400, P600, or other potential arithmetic-related effects during sleep. As suggested by previous non-conscious studies, we predicted that the N400 may be preserved during sleep, but that the P600 should disappear. Brain responses were recorded in both NREM and REM sleep. In REM sleep, previous studies have shown that sensory integration of external stimuli is strongly diminished during phasic REM sleep, when rapid eye movements (REMs) occurs, compared to tonic REM, between periods of REMs (Sallinen et al. 1996; Takahara et al. 2002; Takahara et al. 2006a; Wehrle et al. 2007). We then focused our analysis on tonic REM periods. As a control condition, we presented subjects with the same arithmetic facts during wakefulness just after sleep, with the task to evaluate the correctness of the result. In a second experiment, we also tested the automaticity of arithmetic processing during wakefulness but in unattended condition.

III.3. Results





We first describe the results of experiment 1 comparing the detection of arithmetic violations during wakefulness and sleep (figure 39). Subjects were first presented with correct or incorrect arithmetic facts during their sleep, and then again during wakefulness with the task to answer to the correctness of the result. During sleep, effects in NREM2 and REM sleep are reported.

III.3.1. Effect of arithmetic violations

III.3.1.1. Behavioral analysis during wakefulness

During wakefulness, accuracy in judging the correctness of the result was high and did not differ between operations (Addition [Add]: mean=85.5%, SD=12.7; Multiplication [Mlt]: mean=82.3%, SD=15.1; Subtraction [Sub]: mean=81.3%, SD=15.5; ANOVA between operations: $F=2.5$, $p=0.095$). Reaction times were longer for multiplications than for the two others (Add: mean=739.5 ms, SD=140.8; Mlt: mean=852.1 ms, SD=127.7; Sub: mean=722.9 ms, SD=177.9; ANOVA between operations: $df=32.6$, $p=8.6e-10$; Wilcoxon sign rank test Mlt vs Add: $p=1.2e-05$; Mlt vs Sub: $p=2.4e-04$; Add vs Sub: $p=0.16$). For further analysis during wakefulness, only correct trials were considered.

A. Procedure : MEG/EEG recordings

	SLEEP	WAKEFULNESS POST-SLEEP
Exp. 1	Asleep Arithmetic stimuli Normal pitch No overt task	Awake-attended Arithmetic stimuli Normal pitch correct or incorrect  
Exp. 2	Asleep Unrelated local -global paradigm	Awake-unattended Arithmetic stimuli Modified pitch Low pitch or High pitch  

B. Blocks

Additions

Multiplications

Subtractions

« 4 + 3 ... 7 »

« 5 x 7 ... 6 »

« 9 - 4 ... 4 »

« 8 + 1 ... 2 »

« 2 X 6 ... 12 »

« 5 - 1 ... 4 »

...

...

...

C. Trials

Operation
1300 ms

Result
250-900 ms

ITI
800 ms

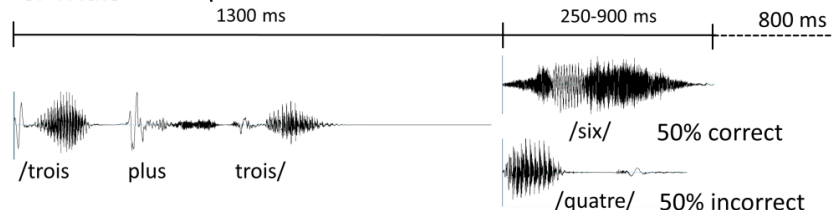


Figure 39. Experimental design

A. Procedure: Experiment 1 probed responses to correct and incorrect auditory arithmetic facts presented for the first time during sleep (NREM2 and REM sleep) and then during wakefulness, while subjects judged the correctness of the results. In experiment 2, the same arithmetic facts were presented during wakefulness, while the subjects' attention was distracted by asking them to respond to the pitch of the voice. B. Block structure: arithmetic facts were presented in three blocks, separately for addition, multiplication and subtraction problems. C. Each trial comprised an operation and a result, which could be correct (50% of trials) or incorrect.

III.3.1.2. Event-related responses

We compared event-related potentials (ERPs) and fields (ERFs) elicited after correct versus incorrect results in the different states of vigilance (wakefulness, NREM2 sleep, REM sleep). In each condition, we start by describing the effect for all operations combined, and then the specific ones for multiplications (Mlt), additions (Add) and subtractions (Sub). All statistical results were computed using cluster permutation tests corrected for multiple comparisons over time and sensor space, within a time-window of 0 to 1.2 s after the onset of the result.

In wakefulness, the arithmetic violation effect was characterized by two successive activations (figure 40). First, an EEG negativity peaked at 316 ms at the vertex (216 to 472 ms, $p=0.005$), followed by a late positivity also starting at the vertex and spreading to posterior areas, from 500 to 792 ms (max. at 656 ms, $p=0.01$). Those activations were very similar to the arithmetic N400 and P600 effects reported in prior studies (Niedeggen et al. 1999; Niedeggen et al. 1999; Núñez-Peña and Honrubia-Serrano 2004). In MEG, significant activations spread from 180 to 512 ms (mag. 192 – 496 ms, $p=0.002$; grad1. 236 – 528 ms, $p=0.011$; grad2. 180 – 512 ms, $p<0.001$, max. at 364 ms) and then from 628 to 796 ms (mag. 628 – 796 ms, $p=0.032$; grad2. 628 – 788 ms, $p=0.017$, max. at 648 ms) in bilateral anterior temporal areas. Time courses and topographies of effects were similar between Add, Mlt and Sub, without interaction between operations.

During NREM2 sleep, analysis revealed a significant effect in MEG only from 268 to 668 ms over right temporal sensors (grad1. 268 to 668 ms, max. 612 ms, $p=0.002$ in right temporal areas) and central anterior sensors (mag. 304 to 508 ms, max. 408 ms, $p=0.003$). ERPs showed a non-significant central negativity whose topography resembled a low-intensity N400. MEG analyses performed separately for each operation revealed slight differences in time and topographies, with effects localized in anterior areas for Mlt (mag. 328 - 476 ms, max. 400 ms, $p=0.031$; eeg. 948 - 1108 ms, max. 1068, $p=0.029$, central areas), in the right temporal area for Add (mag. 436 - 672 ms, max. 624 ms, $p=0.03$ and 696 - 912 ms, max. 760 ms, $p=0.045$; grad1. 568 - 676 ms, max. 624 ms, $p=0.025$) and in the left paracentral area for Sub (grad1. 468 - 548 ms, max. 488 ms, $p=0.042$). Direct comparison between operations showed an interaction between Sub and both Mlt and Add in the left paracentral area (Mlt vs Sub, grad1: 384-536ms, $p=0.032$; Add vs Sub, mag: 700-868 ms, $p=0.049$), and between Sub and Add in the left anterior area (grad1: 248-512 ms, $p=0.001$).

During tonic REM sleep, no significant effect was observed for all operations combined. A significant effect was yet found in Add in anterior areas on MEG sensors (grad1: 1.048 - 1.132 ms, max 1108 ms, $p=0.046$, grad2: 0.984 - 1.044 ms, max 1.032 ms, $p=0.025$). This effect was not present in phasic REM sleep, in line with previous results having shown a deeper processing of sensory stimuli in tonic REM than in phasic REM sleep (Sallinen et al. 1996; Takahara et al. 2002; Takahara et

al. 2006a; Wehrle et al. 2007). However, we were not able to show an interaction when comparing the effects in those two phases of REM sleep, possibly due to the small number of subjects (8 subjects had enough data in both tonic and phasic REM sleep to be analyzed). For purpose of simplification, in further analyses REM sleep will refer to tonic REM sleep.

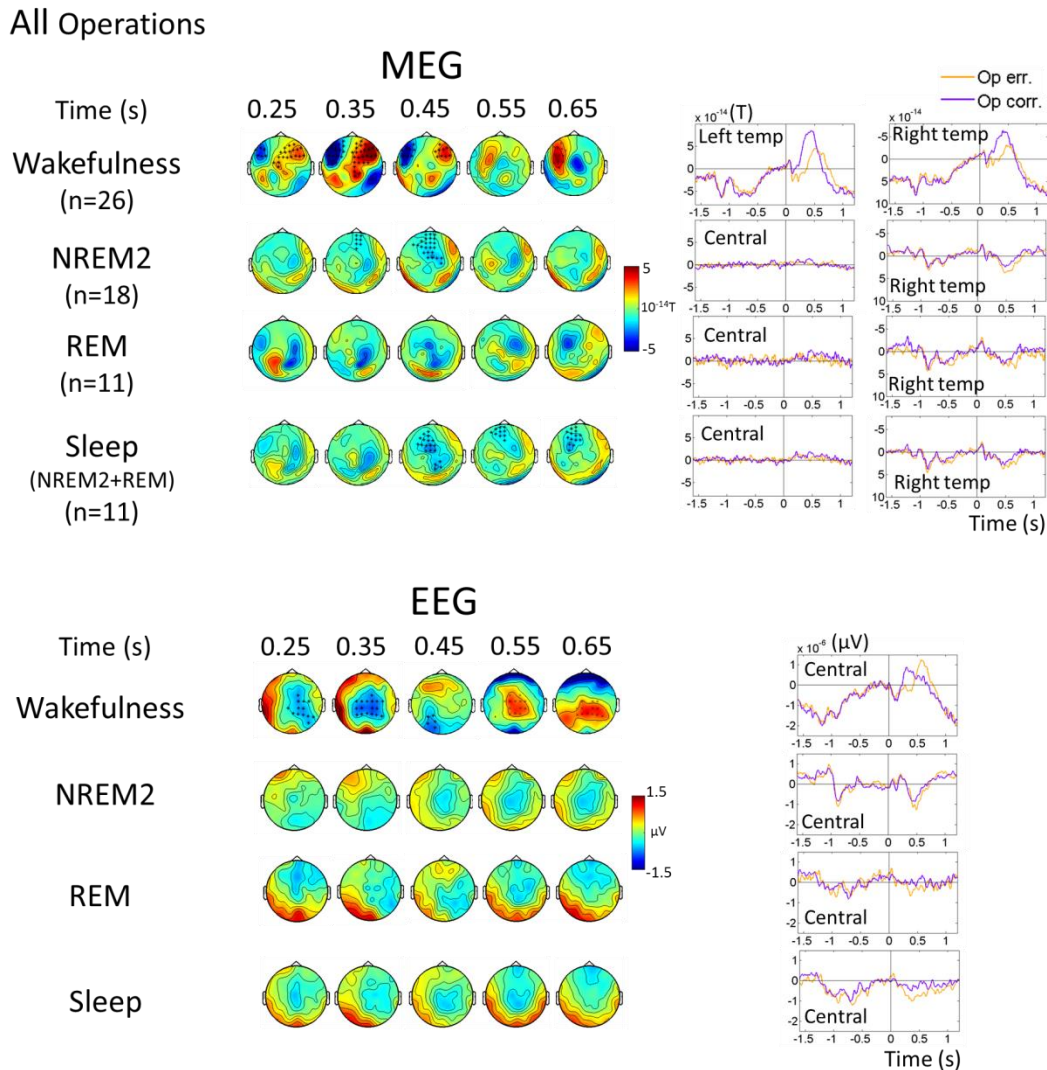


Figure 40. Event-related responses to violations of arithmetic facts during wakefulness and sleep

Graphs at right show the time course of correct (purple) and incorrect (orange) trials (all operations combined) from the onset of the arithmetic fact ($t=0$ is the onset of the result). Topographies of the difference are presented at left (magnetometers for MEG signal). During wakefulness, incorrect versus correct results elicited an EEG N400 component followed by a P600, corresponding in MEG to bilateral temporo-frontal activations. During sleep, a sustained EEG negativity was seen over central electrodes but failed to reach significance, whereas a central MEG effect reached significance in NREM2 sleep and when combining NREM2 and REM sleep.

The direct comparison between the effects of arithmetic violations in NREM and REM sleep did not reveal significant differences. We then assessed whether the arithmetic violation effect could be reinforced by grouping both sleep stages together. Analyses revealed a strong and sustained effect for all operations combined in MEG from 400 ms, from central to anterior areas (mag: 400 – 720 ms, max 460 ms, $p=0.001$), suggesting that both sleep stages shared similar activations. A sustained effect was found for Add in MEG in left temporal and anterior areas in about the same time period, and around 1100 ms (mag: 416 – 584 ms, max 460 ms, $p=0.01$ and 688 – 820 ms, max. 788 ms, $p=0.035$; grad1: 432 – 508 ms, max 456 ms, $p=0.015$ and 1.036 - 1.124 ms, max. 1.104 ms, $p=0.03$; grad2: 412 – 520 ms, max 460 ms, $p=0.011$ and 672 – 788 ms, max. 736 ms, $p=0.023$). In the meanwhile EEG showed a centro-posterior negativity that reached significance later from 800 ms (eeg: 796 - 944 ms, max 856 ms, $p=0.04$). No significant activation was found for Mlt, whereas for Sub early significant effects were found in anterior areas in MEG (196 – 388 ms, max 340ms, $p=0.019$) and in EEG (192 – 388 ms, max 252ms, $p=0.04$, anterior negativity).

We finally assessed the differences of effects between the states of vigilance. The comparison wakefulness versus NREM sleep revealed significant differences in the time window of both N400 and P600 effects (mag. 300 – 432 ms, $p=0.022$ and 632 – 840 ms, $p=0.035$; grad1. 204 – 488 ms, $p=0.007$; grad2. 288 – 464 ms, $p=0.014$; eeg. not significant). The interaction was only found in the N400 time window between wakefulness and REM sleep (mag. 288 – 508, $p=0.016$; grad1.276 – 492 ms, $p=0.008$; grad2 and eeg not significant).

III.3.1.3. Decoding analysis

We also analyzed the effect of arithmetic violations using multivariate analysis methods. Specifically, at each time point, we trained support vector machines (SVM) to discriminate arithmetic violations from control trials. Such an approach presents several advantages: it pools over all sensors, including EEG and MEG, and may thus show increased sensitivity. Furthermore, once a decoder has been trained, we can assess how it generalizes across time and across conditions, such as operations or states of vigilance.

We first trained a classifier to decode correct versus incorrect results for all operations combined during wakefulness. The classifier achieved high accuracy from 184 to 1176 ms (184 - 224 ms, 264 - 960 ms, 992 - 1176 ms, $p<0.05$) (figure 41A, red line). When training different classifiers for each operation, each succeeded in decoding the correctness effect, from 184 ms for Additions and from around 300ms for the others (Add: 184 – 1400 ms with few gaps; Mlt 336 – 776 ms and 808 – 1272 ms; Sub 312 – 824 ms with few gaps, $p<0.05$). As illustrated in figure 3B, classifiers

successfully generalized the effect from one operation to the other, demonstrating that very similar activations occur in all three operations (significant generalization for each successive time point, on the diagonal in fig. 40B.: Add to Mlt: 112 – 776 ms and scattered activations from 792 to 1256 ms; Sub to Add: 176 – 760 ms and scattered activations from 800 to 1280 ms; Mlt to Sub: 104 – 824 ms and scattered activations from 840 to 1296 ms, $p < 0.05$). Matrices of generalization across time (fig 41B) (King and Dehaene 2014) were highly diagonal, suggesting that arithmetic violations induces a series of distinct and short-lived activations. Generalization from Mlt to Sub was slightly displaced above the diagonal, suggesting that activations occur a bit later in Mlt compared to Sub, in line with behavioral results. This might reflect the fact that the duration of multiplication results was on average longer than the duration of subtraction results (ex. ‘72’ as compared to ‘6’), even though all stimuli diverged already at the first syllable.

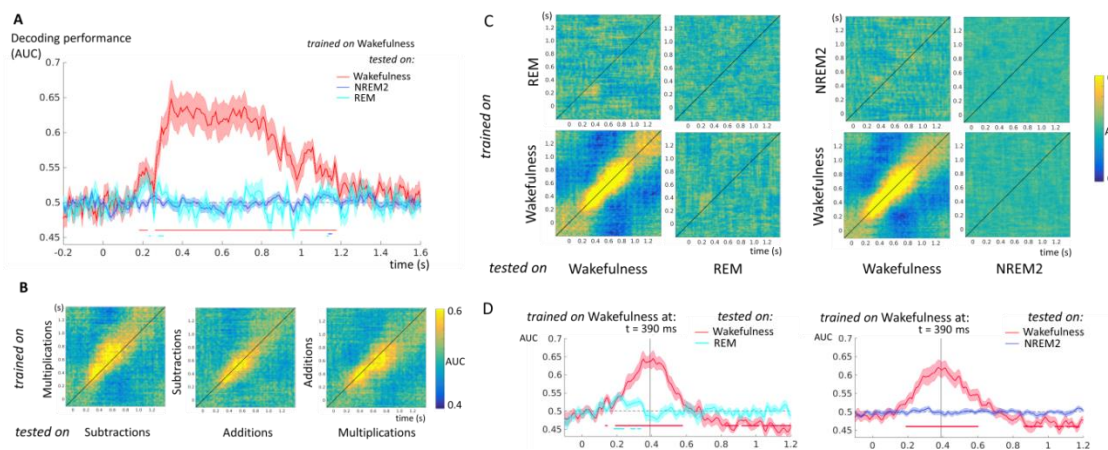


Figure 41. Decoding correct versus incorrect results across states of vigilance and operation types

A. Classifier performance (measured by the area under the curve, AUC) when decoding correct versus incorrect results in wakefulness (red) and when generalizing to NREM2 (blue) and REM sleep (cyan), all operations combined. Horizontal lines next to the x axis indicate significant decoding ($p < 0.05$). Early effects can be generalized to REM sleep. B. Generalization across time within wakefulness: matrices of decoding when the decoder was trained on one operation and tested on another other during wakefulness. Classifiers trained on Mlt, Sub and Add (y axis) are respectively tested on Sub, Add and Mlt (x axis). Decoding performances are represented by increased AUC values (in yellow). Effects are generalizable across operations, indicating that arithmetic violations evoke similar activations for all operations. C. Generalization across time and across states of vigilance. Left: classifiers are trained on wakefulness or REM sleep data (y axis) and tested for generalization within or across states (x axis). Right: same principle with NREM2 sleep. During wakefulness, the pattern of activation follows the diagonal, revealing a succession of activations through time. The early part of this decoding interval generalizes weakly to REM sleep and vice-versa (yellow spot, slightly off diagonal). This effect is illustrated on figure D left for the trained time point $t = 390$ ms in wakefulness: activations at 390 ms in wakefulness are generalizable from 184 to 336 ms in REM sleep. C and D right: No generalization is seen between wakefulness and NREM2 sleep.

We then tested the classifiers trained on wakefulness on both NREM2 and REM sleep. When tested on NREM2 sleep for all operations, the classifier was unable to generalize the arithmetic violation effect in the N400 and P600 time windows. When tested on REM sleep, however, small early generalization effects were seen before 300 ms (232 - 240 ms, 280 - 304 ms, $p < 0.05$) (figure 41A, cyan line). As effects during sleep may occur at different times than during wakefulness, we tested the capabilities of the classifier trained on wakefulness to generalize from each time point to all other time points in the time window (see matrices in figure 41C). We saw that the effect detected between 200 and 450 ms during wakefulness was generalizable to REM sleep between around 200 and 350 ms (figure 41C left). As an illustration, we plotted on figure 3D the generalization effect across the time window when the classifier was trained at $t = 390$ ms during wakefulness, showing that the effect was generalizable to REM sleep from 184 to 336 ms (184 - 240, 280 - 304, 320 - 336 ms, $p < 0.05$) (figure 41D left, cyan line). Such successful generalization from wakefulness to REM sleep also occurred for all training times from 210 to 480 ms. This suggests common early activations between wakefulness and REM sleep, while no such common activation could be detected for NREM sleep (figure 41C and 41D right).

Classifiers trained on each operation during wakefulness and tested on sleep and classifiers trained on sleep failed to report significant effects.

III.3.1.4. Source reconstructions

Sources reconstructions of the arithmetic effect were performed in wakefulness, NREM2 and REM sleep on all operations combined (figure 42).

In wakefulness, early activations started from around 150 ms in bilateral temporal cortices (left superior temporal sulcus, max. 216 ms, MNI coordinates: -51.6 -30.1 -10.5; left temporal transverse sulcus, max. 236 ms, MNI: -42 -33.7 5.7). They then spread to anterior areas, progressively recruiting anterior parts of superior temporal sulci and gyri until temporal poles, along with other semantic-related areas as the left frontal inferior gyrus (right temporal sulcus, max 344 ms, MNI: 45.3 -25.2 -9.3; left planar polar part of the superior temporal gyrus, max. 372 ms, MNI: -41.0 7.6 -28.0; left frontal inferior gyrus, max 368 ms, MNI: -37.3 22.8 10.9). From around 350 to 500 ms, large activations were also found in anterior parts of intraparietal sulci, lateral orbito-frontal cortices, anterior cingulate cortices, insula and entorhinal gyri. After 600 ms, activations were predominant in parietal and prefrontal areas, mainly in right precentral regions (right precentral superior sulcus, max 740 ms and 920 ms, MNI: 29.7 -10.6 49.0).

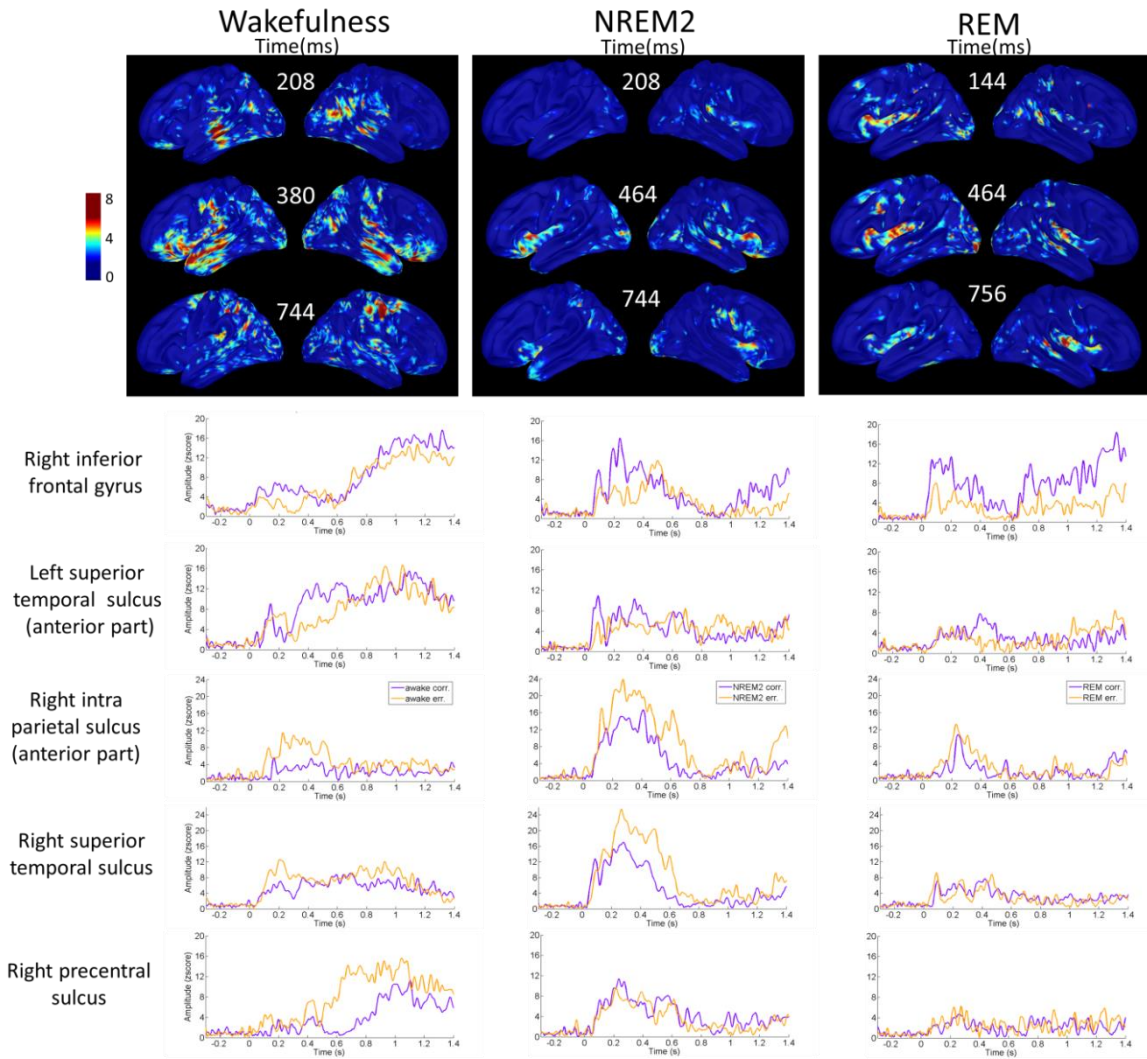


Figure 42. Source reconstructions during wakefulness, NREM and REM sleep

Source reconstructions of correct versus incorrect results and time series of regions of interest are shown for the different states of vigilance. During wakefulness, activations start in auditory cortices, superior temporal sulci and supramarginal gyri. They then spread toward anterior areas of temporal lobes and other semantic and language related areas as inferior frontal gyri to reach a maximum around 380 ms. Late activations are predominant in precentral cortices. During sleep, auditory and semantic-related areas are still activated, as superior temporal sulci and inferior frontal gyri, but in a less extend than during wakefulness.

During NREM2 sleep, activations started in right auditory regions from about 190 ms (posterior lateral fissure, max 228ms, MNI 39.3 -35.2 15.7). They then spread to lateral and medial orbito-frontal cortices, right cingular anterior cortices and entorhinal gyri around 400 ms (right lateral orbito-frontal cortex, max 444 ms, MNI: 27.8 34.0 -7.5), along with sustained activations in the right temporal cortex (superior temporal sulcus and gyrys, max 508 ms, MNI 45.7 -39.8 -1.3), right supramarginal gyrus and right pars opercularis around 600 ms (max 632, MNI 35.9 20.5 12.6). Sources for each operation type are illustrated in figure 45 during significant ERF activations. We can see that additions and multiplications share activations in the right superior temporal sulcus with additional activations

in the right inferior frontal gyrus for multiplications and in the right parietal and precentral cortices for additions. On the contrary, subtractions exhibit localized left intra-parietal activations.

In REM sleep, initial activations also took place near the right superior temporal sulcus, supramarginal gyrus and bilateral auditory cortices (rSTS: max 204 ms, MNI 45.9 -43.5 8.7; right posterior lateral fissure: max 212ms, MNI 42.4 -35.5 14.4). Inferior frontal gyri, insula and the left precentral sulcus were activated around 400 ms (left precentral: max 472 ms, MNI: -32.8 7.6 32.5). During sleep, no late precentral activations were observed.

III.3.2. Effect while the operation is presented

We finally assessed potential differences between wakefulness and sleep during the presentation of operands, before the onset of the result. We indeed could observe on ERF/Ps in wakefulness a progressive drift from the baseline when the operation was presented that seemed strongly reduced during sleep. This progressive drift may reflect some expectation of the incoming result, as it has been described for the contingent negative variation (Walter et al. 1964); it may alternatively reflect processes associated to the computation itself (see also discussion). To test this component during wakefulness and sleep, we then computed the linear regression of ERF/Ps during operations, and tested if its slope diverged from zero and between states of vigilance, across sensors with cluster analysis.

During wakefulness, this progressive drift was strongly significant in large bilateral temporal and frontal areas in MEG (mag, grad1, grad2: $p < 0.001$) and in anterior (negative drift) and posterior (positive drift) areas in EEG ($p < 0.001$). During NREM2 and REM sleep, this drift was still significant in temporal areas (NREM2: mag. $p < 0.001$ in bilateral temporal areas, grad1. $p = 0.01$ and $p = 0.02$; grad2 $p < 0.001$, eeg. $p < 0.001$; REM: mag. $p < 0.001$ and $p = 0.004$; grad1 $p = 0.06$ and $p = 0.002$; grad2. $p < 0.001$ and $p = 0.001$, eeg. $p < 0.001$). However, it was strongly diminished when compared to wakefulness and absent in more anterior areas in both sleep stages, as illustrated in figure 42A (Wakefulness vs NREM2: mag. $p < 0.001$ and $p = 0.032$ in bilateral temporal and anterior areas; grad1 $p < 0.001$ and $p = 0.006$; grad2. $p < 0.001$, eeg. $p < 0.001$ and $p = 0.001$; Wakefulness vs REM: mag. $p = 0.026$ only in right temporal areas; grad1 $p < 0.001$ and $p = 0.034$; grad2. $p = 0.027$, $p = 0.027$ and $p = 0.006$ in both temporal and anterior areas, eeg. $p < 0.001$ and $p = 0.002$). When comparing NREM2 and REM sleep, cluster analysis revealed a stronger drift in REM sleep in the right temporal area (grad2. $p = 0.008$, mag and grad1 non-significant).

The drift in anterior areas observed in wakefulness was actually modulated by the operation type (figure 43B). It was larger for subtractions than for additions and multiplications, with a significant interaction between subtractions and multiplications (grad1. $p = 0.026$) – a modulation that was absent during sleep.

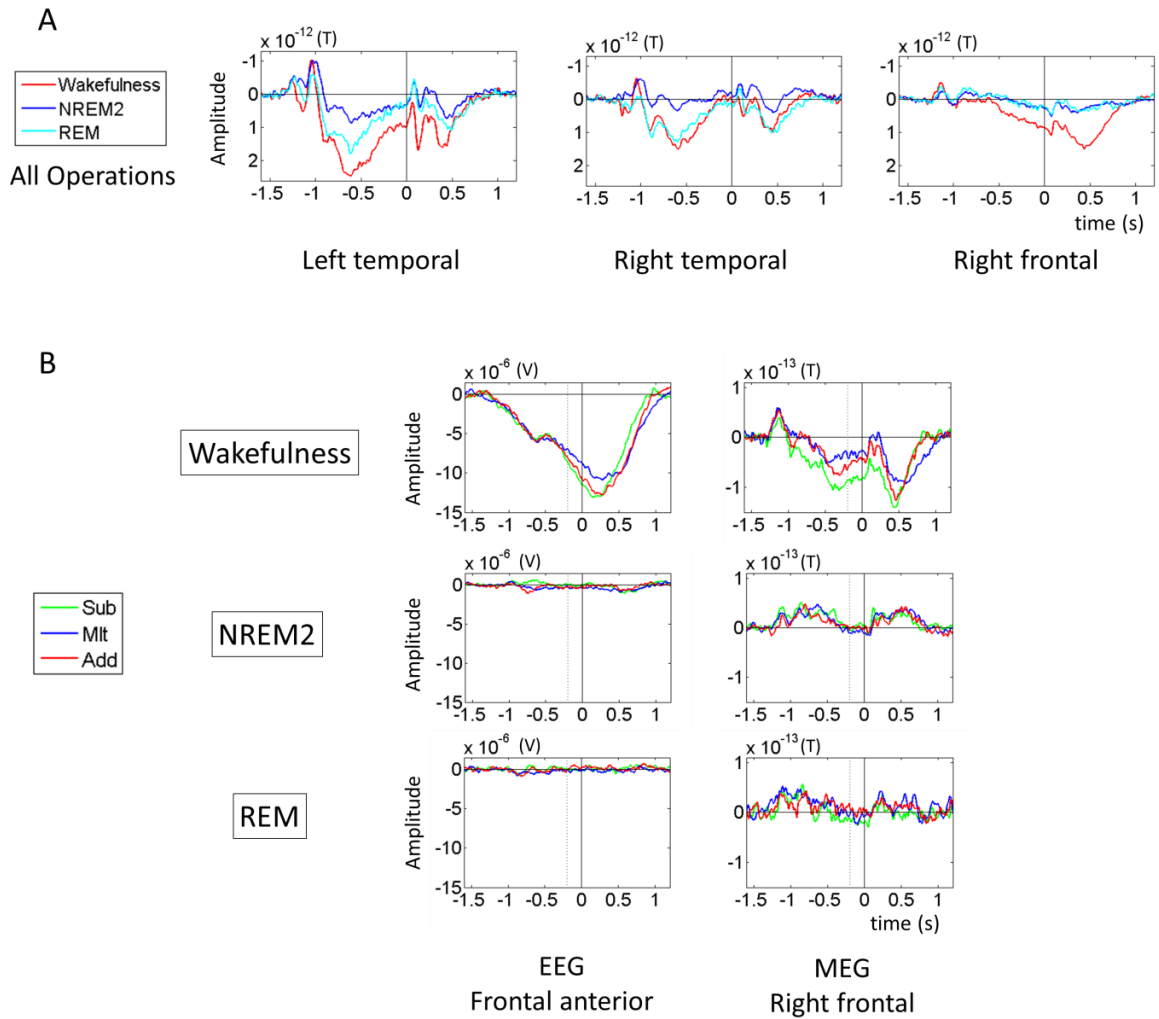


Figure 43. Effect of operation type on sensor-level activity in wakefulness, NREM and REM sleep

A. All operations are combined in the different states of vigilance. During the operation enunciation, a progressive drift from the baseline is visible in evoked responses in anterior areas during wakefulness, while it is extremely reduced during sleep. In left and right temporal areas, ERFs in REM sleep tend to be close to the ones in wakefulness. B. In wakefulness, the drift slope is modulated by the operation type, but not during sleep. The strongest slope is seen for subtractions, followed by additions and finally by multiplications.

III.3.3. Experiment 2: arithmetic violations in unattended condition

In a second experiment, we assessed the capacity to detect arithmetic violations during wakefulness, but in unattended condition. The same correct and incorrect arithmetic facts were presented to subjects, but the pitch of the result was shifted towards lower or higher frequencies. The task was to click with the right or the left hand according to whether the pitch was lower or higher than

the operation. The attention of the subject was thus diverted away from the arithmetic content of the stimuli. We still compared the ERF/Ps effects of correct versus incorrect results (figure 44).

A small but significant effect of arithmetic violations was observed later than in the previous attended condition during wakefulness, from 524 to 712 ms, and localized in left central areas (mag 524 – 608 ms, $p=0.018$ and 612 - 712 ms, $p=0.034$; grad2 528 - 592 ms, $p=0.036$). No significant effect was detected in EEG, but activations corresponding to the significant MEG were represented by a small positivity in very posterior areas. This effect was mostly subtended by additions, as they were the only operation to show a significant effect, from 432 to 628 ms in the left temporal anterior area (mag. 452 - 628 ms, max. 520 ms, $p=0.001$; grad2. 432 - 512 ms, max 504 ms, $p=0.03$ and 532 - 600 ms, max. 548, $p=0.043$). An interaction was observed between Add and Sub in left anterior and central areas (mag. 488 - 564 ms, $p=0.01$).

Interestingly, the slope of the ERF/Ps drift while the operation was presented was strongly reduced in anterior areas, where it was significantly smaller than in the attended condition (mag. $p=0.004$; grad2. $p=0.003$ and 0.02 in right anterior area; eeg. $p<0.001$ in both anterior and posterior areas). Still, an effect of operation was found in those anterior areas, with the same hierarchy than in the attended condition, i. e. a stronger slope for subtraction than for additions, the both having a stronger slope than multiplications (Sub vs Mlt: mag. $p = 0.02$ and 0.003; grad1. $p = 0.008$; grad2. $p = 0.047$; eeg. $p = 0.013$ – Sub vs Add: grad1. $p = 0.003$; grad2. $p = 0.02$ – Add vs Mlt: mag. $p = 0.034$; eeg. $p = 0.004$).

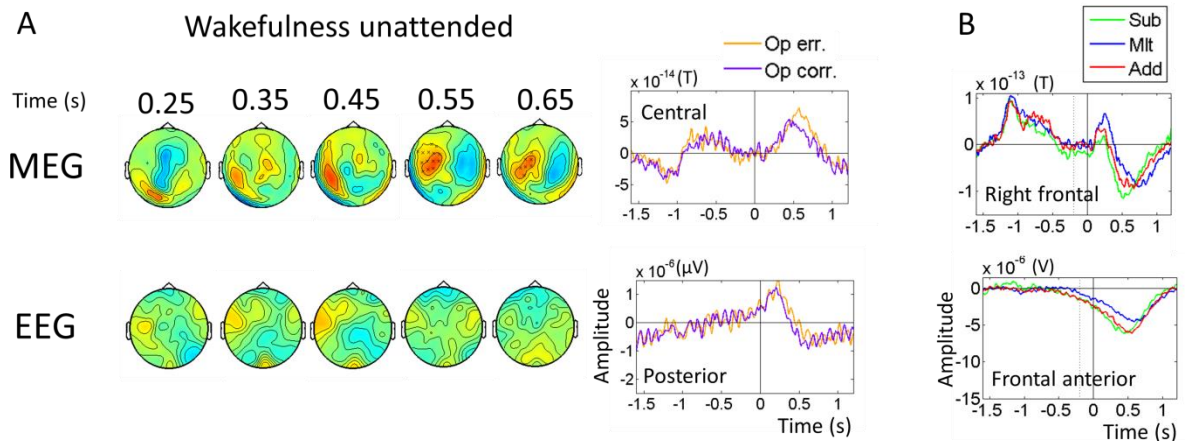


Figure 44. Effect of arithmetic violations in unattended condition and effect of operation type

A. When the subject's attention is diverted from the arithmetic nature of the result, a small late effect between correct and incorrect trials is still seen in left central areas in MEG. B. Average time course for each operation type. During the presentation of the operation, the drift from the baseline is much smaller than during the attended condition (fig. 5B). Yet, this effect is still modulated by operation types, with the strongest effect for subtraction and the smallest effect for multiplications.

III.4. Discussion

The capacity to detect arithmetic violations was assessed during wakefulness, NREM2 and REM sleep. In wakefulness, incorrect versus correct arithmetic facts elicited a succession of N400 and P600 effects, characterized in MEG by bilateral temporal and anterior effects of successive reversed polarity. Those effects were very similar between additions, multiplications and subtractions, and mainly localized to semantic areas in the brain. In sleep, most of the effects vanished. Firstly, no late activations similar to the P600 could be found during sleep. Secondly, most of the N400 also vanished during sleep. Thirdly, the progressive drift from the baseline recorded in wakefulness during the presentation of the arithmetic fact and before the onset of the result was extremely reduced during sleep, and no interaction was seen anymore between operations. Nevertheless, significant activations could still be recorded during sleep in both NREM and REM sleep. In NREM sleep, ERFs showed significant effects between 268 and 668 ms in right temporal and central areas. In the meantime, a non-significant central negativity was found in EEG, of similar topography that the N400, but of decreased amplitude and more spread in time. Despite this significant effect, no decoding generalization could be done from wakefulness effects to NREM sleep. At the contrary, no significant effect was found in REM sleep in ERF/ERPs, but the generalization of the early part of the wakefulness N400 was possible. Those significant results suggest that, while the brain may not be able to perform computation anymore, the detection of arithmetic violations remains possible during sleep, but is reflected by small effects, difficult to extract. Finally, during wakefulness when the attention was distracted away from the arithmetic content, a small late positive effect was found.

Our results during wakefulness confirm previous results of the literature which described a N400-like effect elicited after arithmetic violations, similar to the N400 elicited after semantic incongruities (Niedeggen et al. 1999; Niedeggen and Rösler 1999). In adults, most simple arithmetic facts are thought to be solved by retrieving well-established knowledge from long term declarative memories (Ashcraft 1992). They elicit cognitive mechanism close to semantic retrieval. When the result is presented, several processes can emerge, automatically or not, in order to verify its correctness. First, differences in physical stimulus properties may be detected, such as the phonological features. Second, the arithmetic distance between the result already computed and the one presented may be evaluated, along with activations in the IPS (Dehaene 1999). Third, the parity effect may be evaluated, i.e. whether the parity of the presented result is compatible with the computed one (Dehaene et al. 1993). Fourth, if the arithmetic fact is stored as a sentence, the result will be evaluated in the same way than a word relative to the context of the sentence, i.e. it will be subject to semantic evaluation. Other higher-order processes may also take place, involving strategic expectations, monitoring, or ‘re-analysis’ the

presented result (Niedeggen et al. 1999; Núñez-Peña and Honrubia-Serrano 2004; Szűcs and Soltész 2010; Brouwer and Hoeks 2013; Sassenhagen et al. 2014).

All these effects have been shown to be highly overlapping in both time and EEG topography in the N400 effect (Avancini et al. 2015). Here, source reconstructions from MEG signals, which confer better spatial resolution, precise the spatio-temporal dynamic of the arithmetic N400 effects. The broad and spreading activations from superior temporal sulci and gyri to temporal lobes and inferior frontal gyri confirm the strong involvement of the semantic network thorough the N400. Early activations of auditory areas may be associated to the detection of physical stimulus properties, and later (350 to 500 ms) orbito-frontal, cingular and insular activations associated to error detection. Those sources, first described here in the context of the arithmetic N400, strongly mimic sources of the semantic N400 recorded in MEG (Halgren et al. 2002; Maess et al. 2006). Parietal activations may be more related to the magnitude effect, which nevertheless were not here predominant.

After the N400, a late and sustained positivity starting after 600 ms (P600) from central to posterior regions was recorded during wakefulness, in line with previous studies (Niedeggen et al. 1999; Núñez-Peña and Honrubia-Serrano 2004). In our study, we found activities associated with the P600 in parietal and frontal cortices, sources that are also described for the P3b (Dehaene and Changeux 2011). However, we cannot exclude in our paradigm that part of these activities, such as the ones found in precentral areas, may be associated to motor preparation.

During sleep, no such P600 could be recorded. This result is coherent with previous studies which did not find a P600 in subliminal semantic paradigms (Batterink and Neville 2013; van Gaal et al. 2014). This reinforces the hypothesis that the P600 and P300 share similar mechanisms (Szűcs and Soltész 2010; Sassenhagen et al. 2014; Sassenhagen and Bornkessel-Schlesewsky 2015), and suggest that more generally, late positivities may index conscious processes and vanish in non-conscious conditions.

At the contrary in the literature, EEG negativities that precede those late positivities usually resist to the loss of consciousness. This is for example the case of the mismatch negativity in response to auditory novelty (Allen et al. 2000; Diekhof et al. 2009; Näätänen 1990), the early left anterior negativity after syntactic violations (Batterink and Neville 2013) or, as we saw, the N400 after semantic violations (Holcomb 1993; Luck et al. 1996; Kiefer and Spitzer 2000; Kiefer 2002; Kiefer and Brendel 2006; van Gaal et al. 2014). In our experiment, we did find an effect to arithmetic violations in both NREM and REM sleep. However, this effect was small and the different methods we used did not show clear reproducible patterns of activations.

In NREM sleep, the ERFs significant effects from 268 to 668 ms in central and right temporal areas were not detected by decoding methods: when we tested if ERFs activations were similar to the N400 effects observed in wakefulness, classifiers were unable to generalize decoded effects from

wakefulness to sleep in the time window of significant sleep ERF activations. Two hypotheses could explain those divergent results. First, late effects during sleep are really different to the ones in wakefulness so that no generalization can be performed between wakefulness and sleep. Second, and more probably, activations in sleep are weak and represent only a small part of the broad activations elicited during wakefulness, so that the features used for decoding wakefulness effects are mainly missing during sleep. Indeed, classifiers only focus on the stronger responses and do not take into account all smaller effects. Also, and especially in NREM2 sleep, slow rhythms may introduce important noise at the trial level. At the contrary, the classifier performed well in REM sleep with significant generalization effects from wakefulness before 400 ms. The regain in high frequency rhythms during REM sleep may both promote sensory information integration, and facilitate decoding with much less physiological noise in comparison to NREM sleep. The small number of subjects who reached REM sleep (n=11) may have prevented us to find significant effects in ERFs.

Interestingly, significant evoked responses differed during NREM2 sleep between subtraction on the one hand, and multiplication and additions in the other hand, an interaction that was not observed during wakefulness. Effects were detected around 400 ms in anterior areas for multiplications and between 440 and 600 ms for additions in right temporal regions, but both conditions globally showed the same topographies that did not differ when they were directly compared. Source reconstructions indeed revealed shared activations in the right superior temporal sulcus, with additional right inferior frontal activations for multiplications and intraparietal activations for additions. On the other side, subtractions showed in NREM2 sleep a significant effect in left paracentral areas around 500 ms, corresponding to left intraparietal activations in sources reconstructions. Those differences in activations through operation types may be interpreted as preferential automatic activations of the semantic network for multiplications and additions, and intraparietal activations, possibly reflecting magnitude evaluation, for subtractions. This is coherent with the idea that simple multiplications and additions are mainly stored as semantic knowledge, while subtractions need stronger quantity and number-related manipulations. Thus, the lack of explicit representations and cognitive control during sleep may have revealed subtle differences between operations that were not observed during wakefulness.

Our results then show a small, but significant effect to arithmetic violations, suggesting that the sleeping brain is still capable of detecting arithmetic violations. However, the underlying mechanisms to this detection remain to be clarified. In our experiment, the equivalence between the effects observed and the N400 was difficult to assess. If the topography in EEG did resemble the one of the wakefulness N400, topographies in MEG were significantly different. This could be explained by the preservation of only partial N400 effects, suggested by the small activations in the temporal lobes in sources compared to wakefulness, and by the successful generalization of decoded effects from

wakefulness to REM sleep. However, several hypotheses may be raised on possible underlying mechanisms.

First, we suggest that the real computation of the arithmetic fact is lost during sleep. During wakefulness before the onset of the result, we could see a progressive drift from the baseline in anterior areas that was stronger for subtractions than for additions and multiplications. Notably, this drift was reduced during wakefulness in unattended condition, and strongly reduced with differences between operations abolished during sleep. The differences between operations in wakefulness suggest that the progressive drift, rather than reflecting the expectation of the result that should not differ between operations, is probably associated to the arithmetic computation. We may hypothesize that the cognitive load during computation, especially, should be stronger for subtractions than for multiplications, these last been largely known by heart. This computation would then be lost during sleep, leaving only automatic components.

Then, a few hypotheses may be proposed to explain this automatic error detection. First, the effect of arithmetic violations may reflect the prediction error signal. If the result is not computed during sleep, it could still be retrieved from long term memory and the brain could then anticipate the incoming result. If there is a mismatch between the retrieved result and the presented one, a prediction error signal is elicited. Considering the activations localized to auditory and semantic areas, we suggest that the error signal could result from the evaluation of the phonological features of the result and, possibly, of the semantic context. However, if the hypothesis of a prediction error signal is the one that prevail for the complete N400, we may still suggest alternative hypothesis considering the partial effect during sleep. The effect could be the result of the automatic evaluation of the distance effect (Dehaene 1999), comparing the difference in magnitudes between the intuitive approximation of the result and the presented one, without the need to compute or retrieve the exact result (e.g. in '3+5=1', the exact result is not needed to know that this is incorrect). However, the lesser involvement of intraparietal sulci in our results makes this hypothesis less probable. Finally, we could hypothesize that lower-level processes, such as habituation, may be responsible for the effect. Simple arithmetic facts may be so automatized that, for example, the sequence '3x4' may be stored in the same group of neurons that '12', in sub-cortical structures such as the striatum (Teichmann et al. 2008), leading to a repetition suppression effect when '3x4...12' is presented. However, if the effects observed during sleep reflect such simple habituation mechanisms, it is surprising that during wakefulness in the unattended condition, no early significant effect could be detected. This last experiment suggests that the N400 effect is largely diminished or abolished when the subject's attention is diverted from the arithmetic nature of the results while performing another task. Only late MEG activations with similar topography to the P600 were found for all operations combined. This late positivity probably reflects a conscious executive verification of arithmetic facts after having proceeded to the pitch-related task. We indeed know that when the brain is engaged in one demanding task but need to perform a second

one, it will delay the second task until it has finished with the first one, mechanisms known as the psychological refractory period (Marti et al. 2012). It then suggests that diverting attention to a surface parameter such as pitch may drastically reduce the brain's capacity to detect arithmetic violations. If the arithmetic correctness effect involves habituation processes, it would be surprising that they would vanish in such a dual task.

As a conclusion, we demonstrated that most of the arithmetic violation effect vanishes during sleep. Signatures of computation processes and conscious monitoring failed to be elicited. However, small effects still persist, especially the early part of the N400 effect and activations in auditory and semantic networks. The sleeping brain then still appears capable of eliciting detection error signals for semantic knowledge stored in long term memories.

III.5. Materials and Methods

III.5.1. Experiment 1

III.5.1.1. Procedure

In experiment 1, correct and incorrect arithmetic facts were presented for the first time during sleep and then during wakefulness after sleep, with simultaneous MEG and EEG recording. In order to promote sleep in the MEG room, subjects were asked to sleep only 4 hours the night before (3 to 7 am). Sleep restriction was controlled by actimetry (actiwave 7) measured from 48 hours before the experiment day. All subjects complied with the sleep restriction. They were recorded in the morning for a maximum of 3 hours in the MEG shielded room. Each subject also performed an anatomical MRI.

During the MEG/EEG recordings, subjects were first asked to fall asleep while non-arithmetic auditory stimuli were presented (verbal musical notes presented with the same prosody than the arithmetic facts). They only had to keep their eyes closed and let the sleep come. No information was told about what they will hear during sleep. Once they have reached sleep stage 2 for a few minutes, as indicated by the online EEG monitoring, stimuli were switched to arithmetic trials. The 3 blocks of operations were pseudo-randomly presented (each of the 3 blocks should have been presented the

same number of times before presenting them again). In case of awakening, stimuli were immediately switched back to non-arithmetic ones.

After sleep, the 3 blocks of operations were presented once each with a short pause in between. The subjects were asked to answer whether the result was correct or not by pressing a button with one hand or the other. Hands were counterbalanced between subjects. Subjects were asked to keep their eyes closed all along the experiment, even when awake.

III.5.1.2. Stimuli and blocks design

Additions, multiplications and subtractions were auditory presented in three different blocks, respectively. Each trial was an arithmetic fact, with the operation (first operand, operator, second operand) followed by a result (“7+2...9”), correct or incorrect in 50% of the time. Operands were single digits (1 to 9, zero excluded). The first digit presented was the smallest operand of the two in multiplications and the largest in additions and subtractions (REFS?). The stimulus onset asynchrony (SOA) between the arithmetic fact and the result was fixed to 1300 ms. After the result of a variable duration (250 to 900 ms), the inter trial interval (ISI) was fixed to 800 ms. Each arithmetic fact was presented twice randomly within the block, either followed by the correct result or by the incorrect one (e.g. “7+2...9” and “7+2...4”). Incorrect results were chosen among the set of correct ones for each block of operation, thus ensuring that within each operation, the very same set of words were presented as correct and as incorrect results. An incorrect result was assigned to each operation (see table S4 for complete operation tables). In order to maximize the violation effect, This assignment respected several constraints. The first syllable of the result was phonetically different from that of the correct result, so that the subject could know from the onset of the result that it was incorrect. Also, the incorrect result was never correct under another type of operation (e.g.: “7+2...14”). Finally, to maximize the effect, given that many previous reports have reported an effect of numerical distance between the correct and incorrect results on correctness judgments (REFS), the arithmetic distance between the incorrect and the correct result was maximized (GIVE STATS for each op). We verified that the mean distance between the result and the last operand, and between the result and the mean of the two operands, did not differ between correct and incorrect operations (Multiplications: $p=0.79$ and $p=0.87$; Additions: $p=0.78$ and $p=0.51$; subtractions: $p=0.35$ and $p=0.17$, Welsch's test). As the second operand could be the same digit as the result and lead to repetition effects (e.g. “1x3...3”), incorrect trials were designed to equilibrate those repetitions with correct trials. The multiplication block contained 45 arithmetic facts (90 trials, about 2'30 min). In this block, incorrect results were chosen outside the multiplication table of the operands (e.g.: “3x4...16” avoided), excepted for operands 1 and 2. The addition block contained 40 operations (80 trials). In order to avoid the scattering of the effect through time, only the operations with mono-syllabic results were kept (7+7, 8+6, 9+5, 9+8,

9+9 excluded). The subtraction block contained 36 operations (72 trials), excluding operations where zero was the correct result. Stimuli were normalized for intensity (Audacity 1.3 beta, Unicode Software) and presented at a low intensity of 46 dB (Psychtoolbox software PTB-3, Matlab -R2010a) via the loudspeaker in the MEG room. Literal French music notes that were presented when subjects were falling asleep were assembled to form operands-like and mono or polysyllabic results-like, with the same timing than for arithmetic trials (e.g. “do-si-sol...mi”, SOA between pseudo-operations and pseudo-results 1300ms, ITI 800ms).

III.5.1.3. Subjects

27 healthy, right-handed subjects between 18 and 35 years old were recruited for each experiment (different groups for experiment 1 and 2), on a voluntary basis and after giving written informed consent. The study was approved by the local Ethical Committee Ile de France VII (Comité de Protection des Personnes 08-021). Subjects had no auditory, neurological, psychiatric or sleep disorders and no history of drug abuse. They were selected on their proneness to nap (≥ 1 /week), even in noisy or uncomfortable conditions (train, plane...). They were asked not to drink any exciting drinks (coffee, tea...) or alcohol 24h before the experiment. One subject was discarded from analysis because of magnetic artifacts from dental origin. On the 26 subjects kept for analysis during wakefulness, only those who reached N2 sleep or REM sleep for enough time to present clear auditory evoked potential were kept for analysis (18 subjects in NREM2, 11 in REM sleep). Deep sleep was not reached by enough subjects to be analyzed.

III.5.1.4. Simultaneous M/EEG Recording

EEG and MEG data were recorded with the Elekta Neuromag system set in the supine position (Elekta Neuromag Oy - 204 planar gradiometers and 102 magnetometers) and its built-in EEG system (60 channels). EEG channels were referenced to an additional electrode placed on the nose. Electrocardiogram (ECG), electro-oculogram (EOG) (horizontal and vertical) and chin electromyogram (EMG) were acquired as auxiliary bipolar channels. MEG, EEG, and auxiliary channels were low-pass filtered at 330 Hz, high-pass filtered at 0.1 Hz, and sampled at 1 KHz. Four coils emitting a high-frequency signal were attached to the scalp in order to get the head position relative to the MEG sensor array continuously during the recording. Coils and EEG electrode positions were digitalized before the acquisition with respect to three anatomical landmarks (nasion and preauricular points) with a 3D digitizer (Polhemus Isotrak system).

III.5.1.5. Sleep Analysis

Sleep stages were monitored during the acquisition and re-scored off-line by a sleep expert (M.S.) according to 2007 AASM guidelines (FASST software, <http://www.montefiore.ulg.ac.be/~phillips/FASST.html>). Ambiguous epochs, as transitions between sleep stages, were removed from analysis. During sleep, micro-arousals and K-complexes during NREM2 sleep were manually detected and excluded from analysis.

III.5.1.6. Preprocessing and data analysis

Signal space separation correction, continuous head movement compensation and bad channels interpolation (visually detected) were first performed on MEG data (MaxFilter software, Elekta Neuromag). Cardiac artifacts were removed using principal components analysis. Continuous data were down-sampled to 250Hz and filtered between 0.3 and 30Hz (MNE software, (Gramfort et al. 2014). Trials were then epoched from 300ms before the onset of the arithmetic fact to 1700ms after the onset of the result (Fieldtrip software, (Oostenveld et al. 2011) <http://www.ru.nl/neuroimaging/fieldtrip>). Outlier trials were visually detected and removed from analysis. EEG data for remaining trials were re-referenced to an average reference after bad channel correction. Baseline correction was applied on averages per subjects (300 ms before the onset of the result for effect of correctness analysis, and 300 ms before the onset of the arithmetic fact for effect of operations analysis). ERP/Fs statistical analyses were computed using cluster permutation tests, corrected for multiple comparisons over time and sensor space within a time-window from 0 to 1.2 s. (Fieldtrip software; Monte-Carlo method, 1000 permutations, alpha level for two-side permutation t-tests = 0.025, p value < 0.05 for significant clusters).

III.5.1.7. Source Reconstructions

Current source density estimations of elicited activations after correct and incorrect results were done using MEG signals with Brainstorm software. (Tadel et al. 2011, <http://neuroimage.usc.edu/brainstorm/>). Individual anatomical T1-weighted MRI (3-T Siemens TRIO) were first imported after cortex segmentation (gray-white matter boundary, Freesurfer software, <http://surfer.nmr.mgh.harvard.edu/>). Co-registration between anatomy and MEG signal was done using both head-position indicators and EEG electrodes position previously digitized. Noise covariance matrices were estimated for each subject from empty-room MEG recordings acquired just before the experiment. Overlapping spheres model was used for computing the forward problem. Individual sources were computed with weighted minimum-norm method and dSPM option (depth

weighting factor of 0.8, losing factor of 0.2 for dipole orientation). The correctness effect was obtained after having computed sources separately for correct and incorrect trials and performed the difference of sources. Individual sources of the difference were then projected on a standard anatomical template to perform averages across subjects. Z-score normalization of time series (baseline average was subtracted for each time point and values were divided by the baseline standard deviation) in regions of interest are shown.

III.5.1.8. Multivariate decoding

Multivariate pattern classifiers were trained and tested following the same method as previously described (King et al. 2013a) and using the same parameters as in Strauss et al. (2015). Separate classifiers were trained to discriminate correct from incorrect trials in the different states of vigilance (wakefulness, NREM2 and REM sleep) and blocks of operations (Add, Mlt, Sub and all operations combined). For each analysis, the data consisted in a matrix composed of n trials and f features, where each feature correspond to the amplitude of the MEG signal recorded in a given sensor at a given time point.. The [-200, 1400] ms time window was defined from the onset of the result. Normalization, feature selection, support vector machine and logistic fit were performed within an eight-fold cross-validation scheme. In each fold, the computation were fitted onto $7/8^{\text{th}}$ of the trials (training set) and applied to the remaining $1/8^{\text{th}}$ of the trials (independent test set). Cross validation was stratified in order to keep the same proportion of each trial type in each fold. Decoding performances were represented with empirical receiver operative curve (ROC) analysis and their areas under the curve (AUC). AUCs were computed for each subject and grand-averaged across subjects. Significance was tested within subjects using Mann–Whitney U tests across trials. Across-subjects statistics were computed using Wilcoxon Signed Rank Tests on the mean predicted probability of the true trial class.

III.5.2. Experiment 2

In experiment 2, the same arithmetic facts than in experiment 1 were presented during wakefulness, but the subjects' attention was diverted from the arithmetic nature of the result. 27 subjects were included in the analysis. Stimuli were presented during wakefulness in the same conditions than in experiment 1, after subjects had been sleep-restricted and after a nap in the MEG with simultaneous EEG recordings. However, they were presented during sleep with completely unrelated stimuli (local-global paradigm, see Strauss et al. 2015). The result's pitch was modified to be 40 Hz lower or 40 Hz higher than the operation presented with the original recorded voice (software Praat: doing phonetics by computer, Boersma, Paul & Weenink, David, 2012, version 5.3.15, <http://www.praat.org/>). Low and high pitches were pseudo randomly assigned to have the same

proportion (50% each) in correct and incorrect trials. Subjects were asked to answer as quickly as possible to the pitch of the result by clicking with their right or their left hand if the pitch was higher or lower than during the operation.

III.6. Supplementary Materials

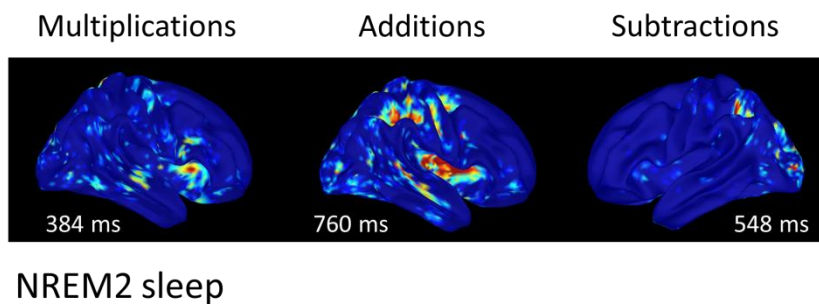


Figure 45. Source reconstructions of different operations during NREM sleep

Source reconstructions of correct versus incorrect results are shown for the different operation types in NREM2 sleep, during significant ERF effects for each of them. Both additions and multiplications exhibit activations in the right superior temporal sulcus. Additional activations are seen in the right inferior frontal gyrus in multiplications and in the right intraparietal and precentral sulci and right insula in additions. At the contrary, activations in subtractions are localized in the left intraparietal sulcus.

Additions	1	2	3	4	5	6	7	8	9
1	6								
2	10	11							
3	12	10	11						
4	10	13	10	13					
5	11	12	12	15	7				
6	13	15	16	3	9	8			
7	12	16	5	9	8	4			
8	6	5	2	7	9		9	11	
9	4	6	7	8		8	10		

Multiplications	1	2	3	4	5	6	7	8	9
1	36								
2	30	27							
3	14	63	24						
4	54	15	48	45					
5	28	21	2	42	18				
6	40	35	56	9	4	20			
7	32	81	36	72	6	10	64		
8	1	25	9	18	6	16	3	12	
9	16	5	8	49	8	7	12	4	24

Subtractions	1	2	3	4	5	6	7	8	9
1									
2	3								
3	4	2							
4	5	3	3						
5	0	1	3	0					
6	1	5	2	3	2				
7	2	0	2	3	3	3			
8	1	2	0	3	3	1	4		
9	1	1	1	2	4	5	3	5	

Table 4. Tables of incorrect results assigned to each operation.

In additions, the few operations with polysyllabic correct results were excluded. In subtractions, operations with zero as a correct result were excluded

III.7. Learning arithmetic during sleep

I take the opportunity of this manuscript to write few lines about a project I carried out during my PhD, related to the previous one but that will not be published, mainly because no significant results could be found. This work has been done with the help of Daphné Rimsky-Robert, a Master 1 student.

We wanted to assess whether the brain could be learn new information during sleep. We presented sleeping subjects with complex multiplications that were either correct or incorrect (e.g. ‘7x12...78’). Only four arithmetic facts were repeatedly presented (2 correct, 2 incorrect) in NREM sleep in order to maximize the putative encoding during sleep. During wakefulness after sleep, subjects were presented with a list of 16 arithmetic facts, with the four already presented during sleep, the four operations presented but with another result – respectively incorrect and correct, and 8 completely new multiplications of the same order of complexity. They had to respond to the correctness of the presented arithmetic facts as quickly as possible (within 1.5 s), using mostly their intuition about the correctness of the result. We did not want they perform the computation, but rather assess the correctness, in order to be potentially more biased by a previous implicit learning. We then assessed whether accuracy and reaction times were biased by the previous presentation of stimuli during sleep, which would have reflected learning during sleep.

A few dozen of subjects were tested with these stimuli, presented within the same acquisition that the previous experiment with arithmetic stimuli. Behavioral analyses on accuracy and reaction times did not reveal any interaction between the stimuli previously presented during sleep versus the one newly presented during wakefulness. Very probably, no learning could be performed during sleep. However, the small number of subjects limits our interpretation.

IV. DISCUSSION

IV.1. Summary of the results

We assessed how deeply external information is processed during sleep using magnetoencephalography (MEG) to record brain responses to stimulations that tested different hierarchical functions in the brain. This exploration of cognitive functions during sleep with MEG in addition to simultaneous EEG recordings was a strong original factor in our work, when compared to previous studies, enabling extraction of precise time courses of evoked responses with a good spatial resolution and an improved signal to noise ratio. This is of considerable importance during sleep, during which strong spontaneous physiological signals can mask small event-related potentials. Moreover, the systematic analysis of hierarchical cognitive functions allowed us to better determine at which step the integration of information is disrupted during sleep, and why a given stimulus may or may not be processed.

In the first experiment, we assessed predictive coding capabilities of future auditory stimuli for arbitrary sequences of sounds. Our results shed new light on processing during both wakefulness and sleep.

During wakefulness, we demonstrated that the well-known mismatch response (MMR), elicited after a deviant sound presented within a series of standard ones (*local deviant*), is actually composed of two partially overlapping but functionally distinct mechanisms: sensory adaptation (habituation) and predictive coding. The early part around 100 ms and the late part after 200 ms reflect sensory adaptation processes and are localized to auditory cortices. The intermediate part, the proper MMN in EEG, reflects the prediction error signal and is associated with large activations in auditory cortices but also in prefrontal regions including the left inferior frontal gyrus. Previous studies already suggested that sensory adaptation (Ulanovsky et al. 2003; May and Tiitinen 2010) or prediction (Garrido et al. 2009; Farley et al. 2010; Wacongne et al. 2011; Wacongne et al. 2012; Todorovic and de Lange 2012) may account for the MMR. Our experiment could confirm that both mechanisms occur during the MMR time window, and precisely disentangle their contributions to the MMR.

During sleep, we demonstrated that:

- Auditory information still reaches sensory cortices. Despite a short delay of about 20 ms compared to wakefulness, early cortical potentials are preserved without amplitude decrease, revealing maintained activations in auditory cortices.

- Sensory adaptation is maintained during sleep. Sensory adaptation was known to take place in sensory cortices (Ulanovsky et al. 2003; Farley et al. 2010; Fishman and Steinschneider 2012) and was found in rats during sleep (Nir et al. 2013). We have confirmed those results in human subjects.

- Consequently to preserved sensory adaptation, the sleeping brain can still detect novel auditory stimuli that break this adaptation. During sleep, local deviant sounds still elicit the early and late part of the mismatch effect.

- Hierarchical predictive coding for arbitrary sequences of sounds is disrupted during sleep. The sleeping brain was not able to extract the regularities embedded in sequences of sounds and to predict forthcoming sounds. The sleep-induced disruption of predictive coding occurred at both the global and the local time scale. Indeed, no prediction error signal was elicited when a new sound violated those regularities: at the local level the intermediate MMR/MMN, and at the global level the P300, were disrupted.

- Loss of the P300 is associated with fading consciousness. During the first stage of sleep (NREM1), the P300 abruptly vanished as soon as the subject became unconscious to the sound. We also confirmed its “all-or-none” behavior.

- NREM1 sleep is a heterogeneous transition stage which contains both conscious and non-conscious states relative to the environment, even within alpha suppression periods.

In the second experiment, we assessed predictive coding of future auditory stimuli for over-learned semantic knowledge stored in long term memory. We tested the brain capabilities to detect violations of simple arithmetic facts. We demonstrated that:

During wakefulness,

- Incorrect arithmetic facts, compared to correct ones, elicit a succession of N400 and P600 effects whose sources overlap those of the well-known semantic N400 and P600.

- Those effects are drastically reduced in inattentive conditions.

During Sleep,

- Most of the wakefulness effects vanish, especially the P600.

- Still, the brain can detect violations of arithmetic facts (for multiplication, addition, and subtraction). Part of the N400 appears to be preserved, suggesting preserved predictive coding for external stimuli that refer to representations already stored in long term memory.

IV. 2. Interpretation

IV.2.1. Signatures of consciousness in response to external stimuli during sleep

Sleep is *a priori* defined as a state of non-consciousness, but how confident can we be with this definition? Could external stimuli be consciously perceived, and then forgotten? Or could they be consciously perceived incorporated in dreams? Those questions are fairly difficult to assess with subjective reports after waking. Reports are dependent upon the integrity of memory encoding during sleep, which has a strong chance of being disrupted considering the deep modifications that occur within the hippocampo-cortical network. This is especially the case during NREM sleep when the hippocampal replay occurs. Complementary assessment of the existence of putative forms of consciousness during sleep may be performed by looking for electrophysiological signatures that have been previously associated with consciousness in literature. Importantly, those signatures are not unconditional markers of consciousness, but they do still provide some information on how deeply information is processed during sleep.

- Late and sustained activations.

The P300 is largely associated with consciousness in the literature (Squires et al. 1973; Squires et al. 1975a; Squires et al. 1976; Vogel et al. 1998; Sergent et al. 2005; Del Cul et al. 2007; Polich 2007) and is believed to index the late amplification and maintenance of information when it accesses consciousness (Dehaene and Changeux 2011). This view has been nuanced by few studies which still reported a small, but significant P300 in non-conscious condition (Bernat et al. 2001; van Gaal et al. 2010a). In our experiment (Strauss et al. 2015), we found that the P300 abruptly vanished at the precise moment when the subjects lost consciousness during the transition to sleep during NREM1 sleep. Our results therefore support the notion that the P300 is a marker of consciousness, which vanishes during sleep. In addition, our results are in line with its already described “all-or-none” behavior when stimuli are perceived or not (Sergent and Dehaene 2004; Del Cul et al. 2007).

The late positivity following arithmetic violations observed in wakefulness, the P600, also vanished during sleep. The P600, which is similarly found following semantic violations, has been compared in term of functional mechanisms to the P300, related to cognitive control and rule violation detection (Szűcs and Soltész 2010; Sassenhagen et al. 2014; Sassenhagen and Bornkessel-Schlesewsky 2015). Our results demonstrating that both P300 and P600 vanish during sleep highlight those similarities and their common vulnerability to the loss of consciousness.

Contrary to those late positivities, it seems that late negativities may be found during sleep. After arithmetic violations, we could record significant ERFs activations after 300 ms which lasted several hundred milliseconds. In EEG, this was associated with a sustained negativity that suggested a partial N400. Previous studies have already shown some evidence for preserved semantic N400 in non-conscious conditions, in subliminal paradigms (Kiefer 2002), in vegetative state patients (Rohaut et al. 2015) and also during sleep (Brualla et al. 1998; Ibáñez et al. 2006; Daltrozzo et al. 2012). Finding an arithmetic N400 during sleep is in line with those previous results.

Generally, it appears that *negativities*, even late and sustained, can persist in non-conscious conditions, but not the late and sustained *positivities*. Actually, only the positivities have been associated with consciousness: those large positivities at scalp level have been interpreted as a massive inhibition via GABAergic interneurons of brain areas that do not participate to the conscious representation, which would dominate over the smaller spot of reverberating activities that are indexed at the scalp level by negativities (Dehaene and Changeux 2011).

- **Distributed activations.** In our experiments, activations elicited during sleep were systematically less distributed than during wakefulness. In our first experiment (Strauss et al. 2015), activations were barely visible in response to violations of global regularities, while distributed frontal, parietal and temporal activations were elicited during wakefulness. Activations in response to local deviant sounds were localized to sensory cortices and the precuneus, while in wakefulness activations spread to large auditory and periauditory areas and prefrontal cortices. Following arithmetic violations, activations appeared more largely diffused outside auditory cortices, but still far less distributed than in wakefulness. These local activations during sleep suggest that the ‘global broadcasting’ of the information associated with conscious access does not occur, at least in our experiments where the violations were carefully tailored to avoid awakening the subject.

- **Top-down recurrent activations.** In our first experiment, the two signals associated with top-down processes, the MMN and the P300, were abolished during sleep. On the other hand, bottom-up processes were preserved, as reflected by the presence of sensory adaptation. In our second experiment, a partial N400 was reported during sleep. We have already discussed its significance in the corresponding section, but if this response indeed reflects a genuine N400, it would advocate for preserved top-down processes during sleep, especially in the context of representations already stored in long term memory. Does the preservation of top-down mechanisms lead to the conclusion that subjects may be conscious during sleep? Actually, top-down activations have already been shown to occur in non-conscious states, for example with the MMN in anesthesia (Koelsch et al. 2006) or DOC patients (Fischer et al. 2004; Daltrozzo et al. 2007; Bekinschtein et al. 2009; King et al. 2011), or through the preservation of cognitive capabilities engaging top-down processing in some DOC patients (Monti et al. 2015). Top-down activations may then be necessary, but not sufficient for consciousness.

- **Information sharing with connectivity or synchrony measures, and metacognition**, were not addressed in our studies. We will come back to this point in the limits and the perspectives sections.

Taken together, the disappearance of late positivities and of distributed activations during sleep in our experiments appears as strong evidence that external stimuli are processed non-consciously during sleep.

IV.2.2. How far is external information processed during sleep?

Novelty detection and Mismatch Negativity

Our results confirm that auditory novelty can be detected during sleep, showing significant MMR to local deviant sounds. However, we demonstrated that the mechanisms responsible for novelty detection were limited to basic adaption processes. No MMN, reflecting top-down processes and prediction capabilities, was elicited by local deviant sounds during sleep. More precisely, the MMN amplitude gradually decreased in NREM1 sleep and was absent from NREM2 sleep. This gradual decrease with the depth of NREM1 sleep was previously described in one study (Nittono et al. 2001).

At the first glance, these results could appear to contradict with other studies reporting a MMN in DOC patients (Bekinschtein et al. 2009; King et al. 2011) or anesthesia (Koelsch et al. 2006). However, in the introduction we have seen that studies actually showed highly varied results and that a significant MMN during anesthesia or in DOC patients was, in fact, not systematic and quite sporadic (Plourde 1991; Simpson et al. 2002; Heinke et al. 2004; Fischer et al. 2004; Daltrozzo et al. 2007; Bekinschtein et al. 2009; Fischer et al. 2010; Faugeras et al. 2012). But interestingly, the MMN, when present in DOC patients, was a good prognostic marker of recovery (Fischer et al. 2004; Daltrozzo et al. 2007 for meta-analyses). It then suggests that the MMN indexes a ‘higher level’ of the non-conscious state, i.e. a state closer to consciousness. Also, its amplitude was found to increase with the level of consciousness, for instance from VS to MCS patients or as a correlate of further recovery (Faugeras et al. 2012; Wijnen et al. 2007). Finally, those results and ours suggest that the MMN does not follow an “all-or-none” behavior as the P300, but rather reflects a continuous process.

We suggest, regarding this gradual increase of the MMN amplitude in correlation to the gradual increase of the level of consciousness, that the MMN reflects a continuous process associated with the gradual transition to consciousness, perhaps indexing the amount of information sharing in

the brain. Information sharing has indeed been shown to progressively increase from VS to MCS and to conscious patients (King et al. 2013b). We hypothesize that a variable recruitment of top-down loops may occur depending on the level of consciousness, leading to modulation of the MMN amplitude. In particular, we suggest that the frontal component of the MMN may be more prone to degradation with the depth of non-conscious states.

This hypothesis could also explain why a small MMN could have been found during REM sleep in some other sleep studies (Atienza et al. 1997; Nashida et al. 2000; Sabri and Campbell 2005; Ruby et al. 2008a), much more frequently than during NREM sleep. Indeed, the increased information sharing during REM sleep, due to the partial regain of arousal with high frequency activities, may have led to the generation of small MMN, barely crossing the detection threshold. We cannot exclude the possibility that in our study the nap protocol may have prevented the occurrence of consolidated REM sleep periods with significant higher level of brain activity compared to NREM2 sleep, and that consequently no MMN could be found. Further studies are needed to clarify this. We will discuss this point in the perspective section.

Detection of arithmetic violations

Our results contribute to enrich the evidence for the existence of significant non-conscious processing. We demonstrated that simple arithmetic fact can be processed non-consciously. Compared to previous priming studies that suggested we could initiate arithmetic rules non-consciously in subliminal paradigm (Galfano et al. 2004; Rusconi et al. 2006; García-Orza et al. 2009; Ric and Muller 2012; Sklar et al. 2012), our results during sleep demonstrate that the entire process of semantic evaluation and detection of violations can be performed non-consciously. Also, compared to other sleep studies, we were the first to show a N400-like effect following arithmetic violations, while all other studies used non-numerical semantic stimuli (Brualla et al. 1998; Ibáñez et al. 2006; Daltrozzo et al. 2012). In the meantime, we showed that associative areas of relevant networks relative to external stimuli could be activated during sleep, such as the semantic network.

If part of the N400 effects remains during sleep, as suggested by our results and others using semantic stimuli, this would mean that the brain is still capable of anticipating the result following the presentation of arithmetic facts (or the semantic category of the forthcoming word following a sentence), and to generate a prediction error signal to incorrect results (or to incongruent words). This appears in striking contrast with the absence of prediction error signal to abstract temporal regularities. We hypothesize that this dissociation reflects a critical difference between our two studies; the use of

novel and arbitrary auditory patterns (experiment 1) versus meaningful representations stored in long term memory (experiment 2).

IV.2.3. What determines the processing depth of external information during sleep?

The depth of integration and processing of external information during sleep appears to be strongly dependent on *i*) ongoing spontaneous oscillations in the brain and *ii*) the nature of the stimuli.

Ongoing spontaneous oscillations. We have seen in the introduction that the integration of external stimuli is modulated by ongoing oscillations. Sensory stimulations are found to be less processed during sleep spindles (Dang-Vu et al. 2011) and, also suggested by our results, during phasic REM compared to tonic REM sleep (Sallinen et al. 1996; Takahara et al. 2002; Wehrle et al. 2007). The high recruitment of thalamo-cortical networks that characterizes those events would then lead to a more efficient sensory gating. In addition, we also suggested that the lack of attention oriented towards the environment during those periods of intense endogenous activity could contribute to decreased information integration. Indeed, during sleep spindles, hippocampal replay occurs along with high gamma activity in the thalamo-cortical network (Steriade et al. 1996; Destexhe et al. 2007; Le Van Quyen et al. 2010). During phasic REM sleep, rapid eye movements, which are supposedly associated with PGO waves in humans, are patterns of activity that are also seen during wakefulness (Brooks 1968a; Andrillon et al. 2015) and believed to be associated with dream mentation during sleep (Hobson and McCarley 1977). Also, subjective report studies suggest that the responsiveness to external stimuli was inversely correlated with dream mentation (Burton et al. 1988). The brain, when strongly engaged in processing internal stimuli, would then be diverted from the surroundings. The sleeping brain could also lack of external attention in consequence of the deactivation of dorsolateral cortices, believed to subtend external awareness processes (Vanhaudenhuyse et al. 2010).

Salience. With the possible exception of when sleep spindles occur, auditory sensory cortices remain responsive to environmental sounds, as demonstrated in our experiment. Most of the time, the first-order relays in the thalamus do not gate the information transfer to the cortex, which can still monitor information coming from the environment. This persistent monitoring of sensory cortices actually appears quite essential to survival in this context of loss of external awareness. As auditory information reaches the cortex, the brain can habituate to sounds and only significantly react to novel or salient sounds. Thanks to such conserved sensory adaptation processes, salience of sensory stimuli is coded in the sleeping brain and may determine information integration.

Knowledge. In the case of abstract stimuli that do not refer to representations already stored in long-term memory, the brain appears not to react beyond sensory cortices, and activations rapidly vanish (Strauss et al. 2015). In the case of stimuli referring to over-known representations, we showed that automatic activations can be elicited in relevant networks and the brain appears capable of non-

negligible information processing such as semantic evaluation and possibly predictive coding. The previous knowledge of presented materials thus appears to be critical for further information integration during sleep.

Relevance. Our studies did not directly assess whether the relevance of a given stimulus could modulate its information integration, but we think it may be an important factor, linked to the previous knowledge. For example, the subject's own name is a classical stimulus which is more deeply processed than other names (Oswald et al. 1960; Perrin et al. 1999), as well as the baby's cry for its mother, or the alarm clock in comparison to the rooster. Relevance then appears important for sensory integration, but it is worth noting that it refers to familiar stimuli that have been previously learned to be relevant during wakefulness. We believe that the stimulus should be *known* to be detected as relevant during sleep, unless it is salient. The relevance factor would then be subtended by previous knowledge. However, the question whether the brain is capable of evaluating relevance during sleep remains open.

If those criteria are met, information has a good chance of being deeply processed through associative areas. But what's next? We can identify at least three options for the evolution of stimuli integration and generated activations. First, the stimulus may simply be processed non-consciously through associative areas, and related activations vanish at some point. Second, it may be incorporated into dreams, i.e. access to the internal consciousness of the sleeper, probably by recruiting more distributed areas in the brain. Third, it may eventually wake up the subject and access the waking consciousness. An outstanding question is then what determines this further processing of presented stimuli: Is it a quantitative modulation of the previous factors? Or is there other qualitative parameters? Also, which activated brain areas may be responsible for the incorporation into dreams versus into waking consciousness? And finally, does the brain judge during sleep whether it is worth waking up or not? Further studies are needed to assess those questions.

IV.2.4. What about the processing depth of internal stimuli?

We saw that external stimuli, especially if they refer to representations already stored in the long-term memory, may be integrated through associative areas, processed into relevant networks and possibly generate top-down activations.

We may then hypothesize that internal stimuli generated during sleep, which are already stored in the brain, are similarly susceptible to deep processing. Actually, they are probably much more deeply processed during sleep than external stimuli. We saw that the replay of memories during NREM sleep, and rapid eye movements/PGO waves during REM sleep, are associated with high frequency activities that reach the level of wakefulness. Also, the content of dream mentation

frequently involves internally generated materials that incorporate memories of stimuli from the environment (Hoelscher et al. 1981; Burton et al. 1988). Internal stimuli can then access a primary form of consciousness, and even sometimes a higher-order consciousness as in lucid dreams with a recovery of metaconsciousness and volitional control (Voss et al. 2009). If those speculations have any validity, then the sleeping brain represents a remarkable dissociation between external and internal awareness.

IV.3. Limits

Several methodological limitations can be raised for this work.

Our main motivation for using MEG in addition to EEG was to benefit from its better signal to noise ratio and its greater spatial resolution. Detecting small effects in the large spontaneous oscillations that occur during sleep may be difficult and limit our investigative possibilities. In MEG, sources are less distributed across the scalp, which may prevent the signal of a given sensor from being affected by any physiological activity that may arise from all over the cortex. Indeed, slow waves, K complexes and spindles are more localized within a group of sensors in MEG than in EEG. However, the fact remains that spontaneous physiological activations introduce noise at the sensor level: for example, spindles may gate the sensory information integration, and K-complexes and slow waves are extremely large potentials that mask the small effects of conditions. We removed K-complexes exceeding $100\mu\text{V}$, but ‘smaller’ ones that are still quite large compared to the signal in wakefulness may still distort our recordings.

Beyond those difficulties of extracting information from physiological activations, an important concern is that if we find an effect, is it the same as during wakefulness, or does it correspond to the same mechanisms? Indeed, the deactivation of some brain regions during sleep may modify the topography of the effects found. For example, if the frontal component disappears, ERP/ERFs topographies may be very different even if other sources are preserved, which may render the comparison between wakefulness and sleep very difficult. In addition to topographies, it may also affect the ability of classifiers to generalize the effects from one state to another. When trained, the classifier extracts the main effects based on the amplitude of the signal at each sensor. If the topography is modified, this distortion may drastically affect generalization. If the main effects of wakefulness are strongly reduced in sleep, the classifier will be unable to correctly generalize. Also, the effect may be modified by superimposed physiological waves. This could explain why some effects observed in ERFs during sleep could not be generalized from wakefulness, especially for NREM sleep.

Source reconstruction can help to find potential common sources between wakefulness and sleep. However, sources performed in our analyses also presented some limitations. We computed sources reconstruction on the MEG signal, which record only the tangential components of current sources. We may have missed other potential radial current sources. EEG captures both tangential and radial sources, but as we had only 60 channels in our EEG cap and we estimated it would be insufficient to get precise sources, we did not compute them.

We did not use measures assessing information sharing during sleep, such as time-frequency and connectivity analyses. We limited our analysis to amplitudes of event-related responses, and some information processing may have been missed with this unique method. Time-frequency and connectivity analyses may be of a great interest to assess information integration both at rest during the different states of vigilance and when comparing evoked responses to different stimuli. Also, our high-density 306 MEG sensors recording is particularly suited to those types of methods. This should be performed in the future, as we will see in the perspective section.

Finally, we only presented here two sets of studies relative to the processing of abstract or over-learned representations. Further studies are needed to replicate our results and confirm (or not) our interpretations.

Beyond those methodological considerations, the indirect approach we used to assess the signatures of consciousness during sleep has also its limits. Those signatures are not definitive markers of consciousness and each of them, taken separately, could have been found in non-conscious conditions. They rather reflect, more confidently, some high level processing, which may still bring some evidence on the depth of information integration. Moreover, those markers still do not answer to the hard problem of consciousness (Chalmers 1995), that of explaining the relationship between physical phenomena, such as information integration, and experience, i.e. our perceptions, mental states or phenomenal consciousness. This hard problem is hard for waking consciousness, and probably even harder for sleep consciousness.

IV.4. Perspectives

From this work, new elements have emerged in the understanding of external information integration during sleep; along with, inevitably, multiple questions that remain to be solved. For some

of the questions that have been raised through the discussion, answers can actually be provided from complementary analyses of our already recorded data set.

First, considering the MMN and the P300, it would be interesting to precisely determine their behavior in the descent to sleep, by analyzing them regarding the different Hori stages of NREM1 sleep. Where is the vanishing point of the P300 (and associated behavioral responsiveness) within NREM1 sleep? Is it the same as the one found for the MMN by Nittono et al. (2001), who described a gradual decrease in amplitude through NREM1 with a vanishing point from the emergence of theta waves? Also, could we replicate Nittono et al.'s results on the MMN? Second, to test if the MMN reflects a continuous marker of information integration, it would be interesting to correlate its amplitude with measures of information sharing.

Information sharing measures have been developed in the lab and have already been tested in DOC patients (King et al. 2013b). One measure, called weighted Symbolic Mutual Information (wSMI), showed a progressive increase with the level of consciousness (from VS to MCS and to conscious patients). In the future, I plan to apply this method to the present sleep data. As previously stated, we could test whether those measures correlate with the amplitude of the MMN. But first, I plan to evaluate wSMI in the different sleep stages. We may predict a progressive decrease of wSMI with the depth of sleep in NREM sleep, and a sudden increase in REM sleep, which will be interesting to compare with wakefulness. Pilot analyses suggest such an evolution through sleep stages, but need to be completed. Also, the distribution of the regions sharing more or less information will be analyzed, as there may be strong differences in information sharing between regions depending on vigilance states, such as between the prefrontal cortex and other regions. In DOC patients, King and collaborators (2013b) showed that the wSMI, measured with high density EEG, increases with consciousness mainly over centroposterior regions, with a topography similar to the P300. Yet, those centroposterior activations in EEG do not reflect activations in the posterior cortex. We do indeed know that EEG has a poor spatial resolution, and we saw in our data that the P300 was actually reflected by anterior activations in MEG. Applying wSMI on MEG data will have the strong advantage, in addition to having even more sensors, to better infer the cortical regions involved. Finally, another step will be to analyze wSMI in response to stimuli in the different conditions, i.e. in response to local and global deviant and standard sounds, or in response to correct and incorrect arithmetic facts.

Still, for assessing information sharing during sleep, another analysis that could be easily performed on our data is time-frequency analysis. We could then test whether the power for each frequency band is modulated by the types of stimuli. Also, we could assess the existence (or absence) of high frequency rhythms in beta or gamma band during sleep, especially during REM sleep.

Those further analyses could provide new interesting data both on sensory information integration during sleep, and on putative signatures of consciousness.

Last but not least, one of my future plans is to apply those methods in the clinics, on patients with sleep disorders. As a neurologist working at a center for sleep and vigilance, I easily see the many potential applications of these tools for improving our knowledge of sleep disorders. If sleep research remains an emerging field, sleep medicine is even more so. In France, sleep medicine is not yet recognized as a specialty in its own right, but attached to departments of physiology, neurology, psychiatry, or pulmonology, despite the extremely high prevalence of sleep disorders in the population. Insomnia, for example, affects about 20% of the population, besides the fact that boundaries between the normal and the pathological are sometimes unclear with regard to sleep. As was the case for sleep research a few years ago, sleep medicine suffers from our ignorance. However, I strongly believe it will very soon be more than an emerging field. We need to transfer the knowledge from the lab to the clinic and go beyond behavioral measures and the outdated sleep scoring of the Rechtschaffen and Kales classification (1968). For example, parasomnia, which we mentioned earlier, is characterized by the regaining of cortical activity in the sensory-motor (and probably limbic) cortices along with the persistence of delta rhythms of large amplitude in frontal areas, well objectified recently in iEEG (Terzaghi et al. 2009). This dissociation is often quite difficult to see in scalp EEG with the very few derivations used in clinics and the diffused rhythms across the scalp. Connectivity measures, including those developed in the lab (wSMI), could be very useful in detecting the modifications of activities across brain regions. It would also be very interesting to apply those methods to narcoleptic patients, who show mixed states between wakefulness and REM sleep, or in patients with insomnia, to try detecting some reactivations which could possibly be responsible for their feeling of hypervigilance, even while asleep.

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