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Cognitive processing during the transition to sleep

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ABSTRACT

Dramatic physiological and behavioural changes occur during the transition from wakefulness to sleep. The process is regarded as a grey area of consciousness between attentive wakefulness and slow wave sleep. Although neurophysiological changes, as the emergence of EEG grapho-elements (spindles, K-complexes), changes in power spectra and coherence, thalamocortical connectivity in fMRI, and single neuron changes in firing patterns, have been well characterised during the falling asleep process, little attempt has been made to link these modifications to the cognitive and behavioural dynamics of the transition. We revise here the body and brain physiology, behaviour and phenomenology of these changes of consciousness and propose an experimental framework to integrate the two aspects of consciousness that interact in the transition, wakefulness and awareness.

Key words

Sleep • Transitions of consciousness • Wakefulness • Awareness • Hypnagogic state

General introduction

Every night we descend unhurriedly in Hypnos arms. How exactly we lose consciousness while falling asleep is far for being characterised. A few studies point to a slow, in the range of minutes, cascade of events (Ogilvie, 2001), while others try to find the "point of sleep onset". This transition from full wakefulness to light sleep manifests in all levels, from molecular to phenomenological, and has its most famous expression in the change of the "Berger wave" (alpha wave) described by Berger when inventing the EEG 80 years ago (Berger, 1940). Every day in thousands of hospitals and clinics around the world, patients fall asleep and most of the data collected between wakefulness and the onset of sleep stage 2 is discarded. Despite long clinical tradition of looking at this transition of consciousness, little scientific research has been done to determine its dynamics. Our aim here was to review the scarce and sparse literature about the process of falling asleep and to build bridges between different levels of explanation and paradigms.

Awareness of the environment and of the self (i.e., content of consciousness) and wakefulness (i.e., level of consciousness) are two aspects of consciousness that are regularly used to separate arousal level from capacity of conscious awareness (i.e. ability to make a volitional response). Classical accounts of consciousness assume that you need to be awake in order to be aware; however, not being aware because you are asleep is the most common, nevertheless interesting case of simple dissociation between these aspects. During NREM (slow-wave sleep) you are difficult to awake and you are unaware (no contents of consciousness), whereas in REM-sleep many people seem to have contents of consciousness (dreams and mentation) but remain difficult to arouse. In both states (REM and NREM) you are asleep (and unconscious) and do

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not behaviourally respond to command, but it seems that awareness is dissociated. Thus, it is clear that differentiating wakefulness levels (asleep/awake states) is by no means the same thing as differentiating awareness levels (conscious/unconscious states). Moreover, the interaction between wakefulness and awareness has hardly been studied. What are the commonalities and differences between the transition from being aware to unaware and the transition from being awake to asleep?

What is sleep, then?

Sleep is normally described as a recurring state of reduced or lack of consciousness, inactivity of voluntary muscles, decreased ability to react to stimuli (as compared to quiet wakefulness), but is more easily reversible than coma, vegetative state or deep sedation. This modern definition is certainly more accurate than those commonly found in textbooks a few decades ago, when sleep was assumed to be simply "a state of inactivity occurring passively when organs became fatigued" (Pelayo and Guilleminault, 2009). More orderly, a short account to decide what is sleep can be found by using these four criteria: a) a state of lethargy (lassitude, inactivity); b) a specific posture (lying down in humans); c) reduced response to stimulation (higher threshold of arousal); d) reversibility, we can wake up from sleep (different from disorders of consciousness).

Sleep is also described in terms of the two-process model of sleep regulation, the interaction of the homeostatic Process S and the circadian Process C (Borberly et al., 1982; 2005). The ultradian process completes the picture by representing the two main sleep stages (REM and NREM). The model is good in the scale of days and can predict the contribution of homeostasis and circadian Clock in sleep patterns. However, for the cognitive dynamics of the sleep onset process -the purpose of this review- there are no established models that we could bring to help in the explanation, although we will discuss some simple models that could soon become a tool to look at transitions.

Emergence and physiological mechanisms of sleep cycles

In the history of evolution, before animals began to sleep they were already cycling. First, there was circadian rhythmicity, and sleep evolved later, possibly when the community of neurons (in simple chordates) became big and complex enough to profit from new functions complementing the circadian clock.

Wakefulness cycles exist since the moment a molecular feedback loop evolved hundreds years ago under the pressure of the light-dark cycle (Dvornyk et al., 2003). In mammals the central circadian clock that time us is in the base of the hypothalamus, a few thousands cell in the suprachiasmatic nucleus (Schwartz, 2009). Sleep is under strong circadian regulation but its molecular and cellular mechanisms have become more widespread that the central circadian clock itself (Zimmerman et al., 2008). Wake-sleep cycling seems to be controlled by the interaction between the anterior hypothalamus (where the central clock sits) and more ventral and lateral parts. The ventrolateral preoptic nucleus possibly sets off sleep onset by mutual inhibition of arousal systems in the brainstem, the posterior hypothalamus and basal forebrain. These networks are most likely closely modulated by the orexinergic arousal system of the lateral hypothalamus (Pace-Schott and Hobson, 2002). These structures are not directly accessible in humans, posing limitations to unravel the cellular and molecular mechanisms of changes of consciousness states.

Physiological modifications at sleep onset

Sleep cycle progression is reflected in every biological level of organisms. Thus, a set of changes can be observed at the physiological level while approaching sleep.

The most notorious and studied of these modifications is probably the appearance of slow rolling eye movements (SEMs) during the state of drowsiness, which ceases before the first sleep spindles (Hori, 1982; De Gennaro et al., 2000; Oglivie, 2001; Magosso et al., 2007). These SEMs have been closely related to the EEG spectral changes associated with sleep onset (SO), and peak just before the cessation of behavioural responsiveness (Ogilvie, 2001). They are also simultaneous to another sleep related physiological modification, namely the decrease observed in skin potential negativity (Hori et al., 1982; Susmakova et al., 2008).

Thermoregulation is also modulated. The core body temperature decreases before sleep onset, along with an increase in peripheral temperature (Van Den Heuvel et al., 1998). Furthermore, the balance between the two components of the autonomous nervous system is reversed during the sleep onset period, with the parasympathetic influence becoming dominant, resulting in a decreased heart rate, even before the onset of classic sleep stage 1 (Baharav et al., 1995; Pivik and Busby, 1996). Respiratory activity is also reduced, the decrease happens in parallel to the alpha to theta EEG power dominance shift characteristic of sleep onset (Worsnop et al., 1998), and to the slowing of reaction times (Ogilvie et al., 1989).
All these physiological modifications appear thereabouts in parallel before the onset of classical sleep stage 1. Hence, it is tempting to suggest that they are subserved by common underlying mechanisms of sleep onset anticipation.

Neurophysiology and the brain signatures of falling asleep

The change in conscious state at sleep onset is accompanied by complex neurophysiological changes, classically studied through EEG/polysomnographic recordings. The transition is characterized by many neurophysiological changes, some of them directly noticeable in the EEG. But there is more to oscillatory brain activity than meets the eye.

Spontaneous electroencephalographic fluctuations

The brain signatures of sleep onset are well characterised in scalp EEG and give rise to the definition of sleep stages that are now accepted by the clinical sleep societies worldwide (Silber et al., 2007). Nevertheless staging still has a high degree of subjectivity since it relies on visual scoring; and despite humans are excellent at pattern recognition, the variability of experts rating the same sleep polysomnographic recordings is huge (Danker-Hopfe et al., 2009). As it happens with any defined measure, there are arbitrary components and the classic sleep staging system is no exception. To further characterize the transition it is necessary to make use of finer grained measures. Under the current criteria, 20-30 seconds are the minimum units to define the stage, but it is clear from any EEG measures and from the timing of the cognitive processes that this period may contain several microstates (Hori, 1985). Since several time scales of changes can be defined in the transition between being asleep and being awake (tonic, phasic and transient) (Makeig and Jung, 1996), research should benefit from shorter and richer measures.

Qualitative EEG patterns during the transition

Hori and collaborators acknowledged the time scale limitation of using 30sec epochs more than 20 years ago, and created a visual scale relying on the graphoelements defined in the classic scale. Theta and alpha waves, vertex shape waves, k-complexes, spindles and slow wave rhythms were used to generate a scale (the Hori Scale) taking 5 seconds as the minimum unit and using a broader coverage of the scalp.
Nine Stages were defined in this manner, from drowsy (H1 and H2), to classical sleep stage 2 onset (H9) and the appearance of sleep spindles. In between, the heterogeneous period classically defined as sleep stage 1 was detailed in six stages (H3 to H8) characterised by different EEG patterns (Hori et al., 1994). Along the falling asleep process, spontaneous EEG activity present a stage by stage evolution along this nine step scale, but this succession is not strict and uniform across all subjects, as some stages can be unstable or even absent from the sequence (i.e. H4, H6, and H1H2H3 for subjects with suppressed alpha) (Tanaka et al., 1996; Oken et al., 2006).
The Hori system represents an improvement in the characterisation of the sleep onset period compared to classical scoring methods in that it permits a refined description, sensible to microstates. This makes it a potentially useful tool for clinicians. Nonetheless, because it relies on non stationary and artificial material (short epochs) and on subjective and non systematic pattern recognition, it is somehow not fully satisfying for a scientific study of the transition in different states of consciousness.

Quantitative electrophysiological measures of the transitions

Despite the strong bias of “clinical sleep” to define sleep in terms of qualitative eyeball EEG patterns, EEG spontaneous activity at sleep onset has been frequently studied through power spectra analysis.

This non-stage based approach, based on mathematical tools, meets the criterion of objectivity and allows a dynamic and continuous description of the changes. The three major sleep rhythms (Steriade, 1993) are increasingly reflected in EEG activity while entering sleep: slow oscillations (< 1 Hz), delta, and spindle activity. More precisely, delta and theta activity increases substantially, while high frequency activities decrease (Fig. 1). In particular during the wake-sleep transition, alpha activity shows a dramatic decrease, the peak in the topography becomes more anterior, and its peak frequency shifts (Tanaka et al., 1997). A rise in sigma activity, linked to the synaptic generation of sleep spindles in thalamic networks (Steriade, 1993) is, on the contrary, observed at late stages of the sleep onset process (Tanaka et al., 1998; De Gennaro et al., 2003).

Yet another interesting set of measures arises from the analysis of the frequency bands coherence, providing rich information on the synchronisation of brain oscillations, and the changing relationships between different regions of the cortex at sleep onset. In particular, these studies signal a modification of the functional association between frontal and posterior areas (Ogilvie, 2001). Globally, coherence increases while progressing towards sleep, but shows a transient decrease around Hori stage H4, that could correspond to the switch between alpha and theta dominance. While a significant decrease in alpha fronto-occipital and inter-frontal coherence is observed during drowsiness (Cantero et al., 1999), delta and theta coherence increase in antero-central areas from H6 (Tanaka, 1999). On the other hand, sigma coherence emerges in the central area around H8, before spreading to the whole cortex (Tanaka, 1998).

A promising tool for a systematic measurement of EEG spontaneous signals change, and automatic detections of sleep onset, is the use of non linear mathematical methods (e.g. correlation dimension, fractal exponents). These measures highlight signal complexity decreases at sleep onset (Acharya, 2005; Susmakova, 2006; 2008).

Altogether, these EEG measures show that spontaneous brain signal is dramatically modified while progressing towards sleep. The loss of consciousness and vigilance is paralleled by the transition from a high frequency and complex mode, to a slow oscillatory and highly synchronized mode.

Evoked EEG potentials during the transition

Another way to look at brain signal is to observe its reactions to perturbations, instead of its spontaneous evolution. This is done in electroencephalography by computing event related potentials (ERPs), and in particular in the sleep domain ERPs provoked by the presentation of auditory stimuli (auditory related potentials, ARPs).

Like spontaneous activity, neurophysiological response to stimuli is modified early in the transition. Thus, ARPs (P1, N1, P2, N2 components) recorded after tones presentations during the sleep onset period show gradually increasing modifications with the progression towards sleep. While the amplitude of N1 is gradually attenuated, the amplitude of P1 and P2 increase (Noldy et al., 1988; De Lugt et al., 1996; Ogilvie, 2001). De Lugt and collaborators proposed that these modifications result from the attenuation of a negative slow wave with the progression towards sleep (alternatively it could be that a slow positive wave is added to the waveform). This slow wave could reflect differential mode of processing depending on vigilance states. Results concerning the N2 component are less clear: some studies found increased amplitude as sleep progresses (Ornitz et al., 1967; Harsh et al., 1994; Ogilvie, 2001), but others didn't find modifications of this component at sleep onset (Noldy et al., 1988; De Lugt et al., 1996). Later components (N3, P3) on the contrary show consistent and dramatic increases with sleep progression (Ogilvie, 2001). Furthermore, the end of the transitional period sees the emergence of specific components (N350, N550) that are related to transient sleep patterns such as the evoked K complex characteristics of sleep stage 2 (Harsh et al., 1994; Atienza et al., 2001).

A few studies, using classical oddball paradigms during the sleep onset period, have focused on the P300, a neurophysiological signature of the detection of infrequent stimuli. They found that with sleep progression, P300 amplitude is gradually reduced, and that this reduction is tightly linked to behavioural responsiveness and target detection (Harsh et al., 1994; Cote et al., 2002). Studies that focused on the MMN, that is supposed to reflect automatic change detection mechanisms, show a gradual diminution of the MMN with sleep progression (Nittono et al., 2001; Sabri et al., 2003). According to Nittono and collaborators, the MMN

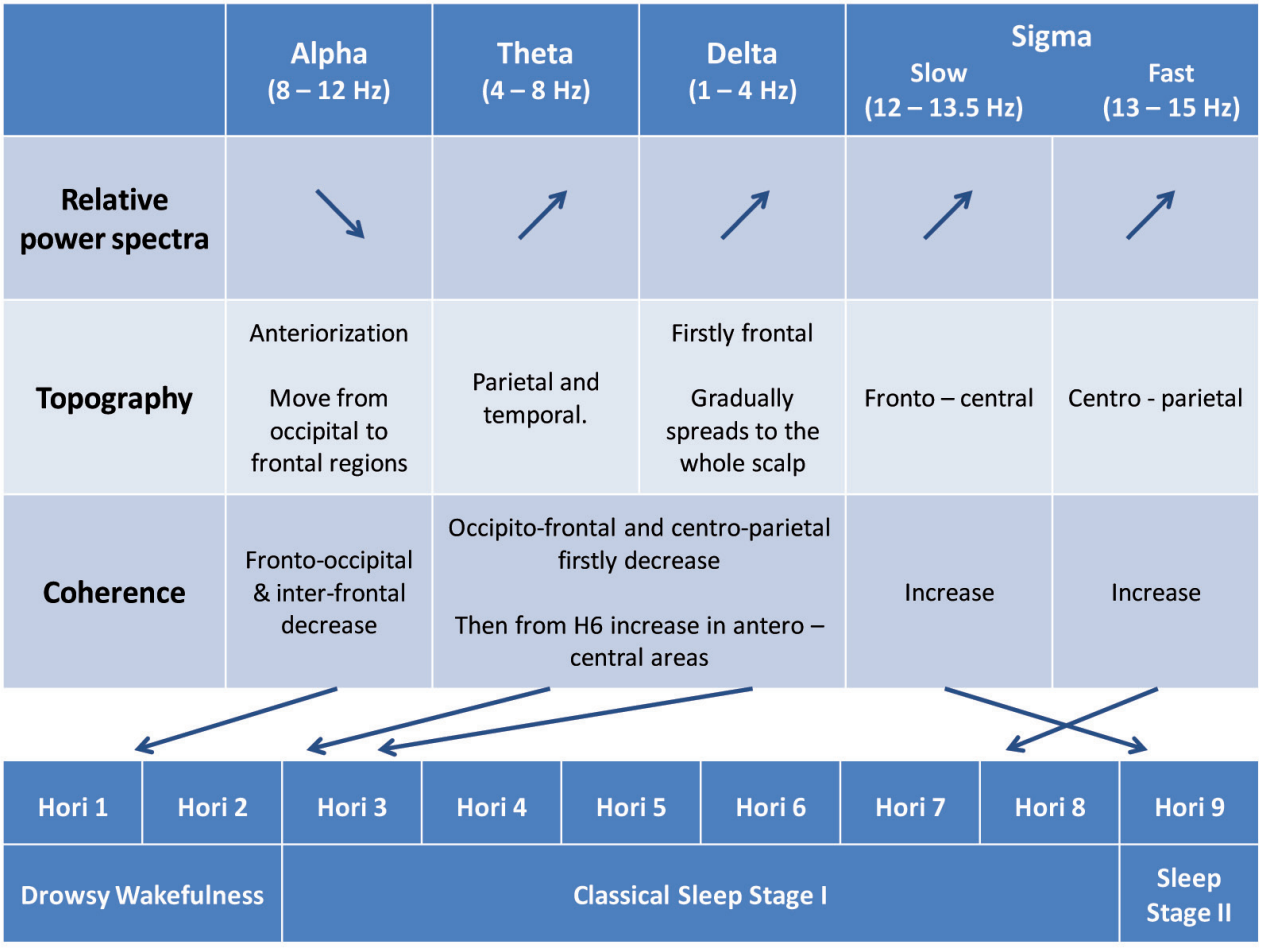

Fig. 1. - Spontaneous electroencephalographic modifications at sleep onset. EEG relative power spectra, topography and coherence evolution along sleep stages for relevant frequency bands. Sources: Hori et al., 1985; 1994; Tanaka et al., 1997; Tanaka et al., 1998; 1999; Cantero et al., 1999; Ogilvie, 2001; Oken et al., 2006; Susmakowa et al., 2008.

vanishes around Hori stage 5 (Nittono et al., 2001). However, other studies still find a MMN in response to large deviants throughout sleep stage 1, and even in sleep stage 2 (Atienza et al., 2002; Sabri et al., 2003; Ruby et al., 2008). These differences probably result from methodological divergences (rate of stimuli presentation, intensity of the tones, sleep stages definitions, computation of the MMN, confusions with the N1 component of the ARP…). These studies nonetheless suggest a gradual attenuation of change detection systems while subjects fall asleep. Whether this impairment is linked to the attenuation of environmental signals at the thalamic level, or to further cognitive steps of stimuli processing (e.g. sensory memory, comparison mechanisms…) is far from clear.

Hemodynamic activity during the transition

Passive transitions with spatial neuroimaging

In light sleep stage 2 (regarded as the stage of true loss of self-conscious awareness) there are several areas showing decreased activity, as measured by BOLD signal, when compared to rested wakefulness. Thalamus and hypothalamus, cingulate cortex, right insula and adjacent regions of the temporal lobe, the inferior parietal lobule and the inferior/middle frontal gyri, all showed deactivation in stage 2 (Kaufmann et al., 2006). Interestingly, in sleep stage 1 there were commonalities to stage 2 but when compared directly (direct contrast) S1 showed more activity than S2 in the middle and MedFG, supramarginal gyrus, superior temporal gyri, cingulate cortex, supplementary motor area and paracentral lobule. In contrast, S2

showed more activity in the cerebellum, the parahippocampal gyrus and the hippocampus. Although difficult to interpret directly, these activations and deactivation seem partially replicable (Kajimura et al., 1999), S1 (Kjaer et al., 2002), S2 (Andersson et al., 1998; Maquet et al., 1992, 1997), and they may become more powerful when compared to TMS-EEG and intracranial studies of transitions.

In another series of studies the relationship between EEG power bands and localized brain activity started to be established. Specifically, delta activity covaried negatively with rCBF (PET) in the thalamus and brainstem reticular formation, cerebellum, anterior cingulate, and orbitofrontal cortex (Hofle et al., 1997). In the second analysis, when the effect of delta was removed, a significant negative covariation between spindle activity and the residual rCBF was evident in the medial thalamus. In a study using EEG-fMRI Laufs and collaborators (Laufs et al., 2007) found a negative correlation in alpha band with BOLD changes in the precuneus, prefrontal, and temporal-parietal cortices. Thalamus activation was correlated with sigma power and negatively with central alpha power. The authors tend to interpret these covariations with the active inhibition of thalamocortical relay neurons in association with slow wave rhythms and spindles, as well as the neural substrates underlying the progressive attenuation of sensory awareness, motor responsiveness, and arousal that occur during slow wave sleep. We extend this interpretation to current frameworks of integrative processing by suggesting that dissociation of networks during the transition, with decreasing frontoparietal activity from awake to S1 to S2 fits nicely with the hypothesis supporting loss of integration in the attentional network as we fall sleep.

More support for the thalamocortical role in information integration and sleep transitions comes from the analysis of the local and long-distance functional connectivity. While from awake to light sleep the thalamocortical connectivity brusquely decreases, the corticortical interaction increases (Spoormaker et al., 2010). Moreover, local processing seemed to be almost random in light sleep while slow wave sleep correlated with a high degree of local clustering.

Active transitions with spatial neuroimaging

Single neuron studies have frequently reported a decrease in activity in primary cortices in response to stimuli during SWS in mammals (Issa and Wang, 2008). Nevertheless, the results are mixed for the auditory modality. Some studies found a reduction of activity during sleep (Murata and Kameda, 1963; Brugge and Merzenich, 1973), while others found the opposite effect, with even increased activity during sleep (Peña et al., 1999; Edeline et al., 2000). These findings are supported by an early fMRI imaging were auditory cortex activation did not change between sleep and wakefulness when presented with by simple tones and the subject's name (Portas et al., 2000). Others have shown decreased activation in the auditory regions of the temporal lobe during sleep (Czisch et al., 2004), more specifically, BOLD decreases were higher during stage 2 but vanished in slow wave sleep. Deactivations in auditory areas were associated with increased number of K-complexes and delta power (Czisch et al., 2004). Following these results Issa and Wong (Issa and Wong, 2008) found, in monkeys, that modulation was heterogeneous across neurons such that responses in sleep could be enhanced, suppressed, or unchanged compared with wakefulness. This variability in cortical effects in primary and secondary cortices founds its counterpart in EEG and behavioural responses in human (see above). One possible interpretation is that BOLD correlates more with synaptic activity than spiking activity measured extracellularly so if imaging signals are dominated by the depressed input coming from thalamus in light sleep, they may not reflect active cortical processing during sleep.

Another interesting result arises from the study of sleep spindles. These may be a key component in information processing during Sleep stage 2 (Schabus et al., 2007), thought to be associated with the alteration of consciousness in this stage. Spindles are 11 to 15 Hz oscillations lasting for 0.4-3.5 seconds, arising from rebound spike bursts in thalamocortical neurons postinhibition by reticulothalamic neurons (Steriade and McCarley, 2005). While together the spindles activate the thalami, anterior cingulate cortex, insular cortex and superior temporal gyri, when differentiating the slow and fast spindles, slow spindles seem to involve activity in the superior frontal gyrus, while fast spindles recruited a set of cortical regions involved in sensorimotor processing, as well as the mesial frontal cortex and hippocampus.

Intracranial recordings and TMS induced sleep waves

A recent study showed that the thalamus precedes the cortex by several minutes in the progressive deactivation leading to deep sleep (Magnin et al., 2010). The authors use a measure called dimension of activation (Shen et al., 2003), which provides an index of EEG signal complexity, higher in wakefulness than during slow-wave sleep, and independent of the amplitude of the signal. DA permits the temporal analysis of activation changes in each electrode. In the original studies in lab animals Steriade and collaborators (Steriade et al., 1993) did not find an earlier area originating the development of slow wave rhythms but they suggested this rhythm starts in mesopontine nuclei or locus coeruleus neurons with a relay in the thalamus which spreads the message to the cortex. Magnin and collaborators add the temporal dimension to this mechanism by elegantly showing that the early deactivation of the thalamus, as measured by local field potentials in humans, is followed by different areas of the cortex. This effect of earlier sleep onset by the thalamus seems to be true for the initial microstages from awake to early onset of the Sleep Stage 2, while changes in DA from stage 2 to 3 or 4 do not show delays. Another major finding is that those delays found in transition from wakefulness to light sleep do not appear when the patient regains consciousness, in the transition from sleep to awake. The transitions are not symmetrical.

In a key series of studies Tononi and collaborators used a perturbational approach to evaluate the integration capacity of the brain in different sleep stages (Massimini et al., 2009). They used a combined TMS-EEG technique and applied faint TMS pulses to the frontal cortex. This allowed them to show that the brain wave elicited by the pulse travelled to distant areas during wakefulness (even crossing hemispheres) but remained local in Stage 2. In stage 1 there was a middle ground with partial cortical neuronal activity, processing of sensory inputs and sometimes displays patterns of synchronous activity (Massimini et al., 2005). According to Tononi's model what happens as consciousness fades is that the brain looses integration and differentiation, and breaks down in modules, local cortical processing, or generates a common nonspecific response in the form of a (sleep) slow wave (see this volume).

A recent experiment by this same group of researchers, (Vyazovskiy et al., 2011) showed that in freely behaving rats awaken for a long period, cortical neurons can briefly and locally go "off-line" (stop firing altogether and display high-amplitude slow waves) as in sleep. These striking results suggest that the process of falling asleep is even more widespread in time and space than previously thought, as independent groups of neuron can already exhibit a sleep like pattern in a fully awake state. Experiments using a combination of high density EEG, intracranial recordings, behavioural and responsiveness measures are needed to extend the results to humans and further characterize these "local sleep" events.

Behavioural dynamics of falling asleep

At sleep onset, subjects progressively lose the ability to respond to external stimuli. The complete loss of responsiveness constitutes a behavioural sleep onset, assimilated by a few authors to the loss of awareness.

Behavioural sleep onset has been classically studied through active or passive paradigms. In active paradigms, subjects must press a button after an auditory cue. Behavioural sleep onset is then achieved when a consistent absence of responses to environmental stimuli is observed. In passive paradigms, subjects must exert a continuous pressure on a button. Behavioural sleep onset then corresponds to a release of the pressure. These two methods correlate, but according to Ogilvie (1985, Phd Thesis), the loss of responsiveness measured by passive method is more sensible and occur before the one measured by active methods. This could be linked to the awakening power of the tones commonly presented in active paradigms.

Studies using the active paradigm point out a gradual augmentation of reaction times with the progression towards sleep (Oglivie and Wilkinson, 1989; Hori et al., 1994). This slowdown is observed from early stages of drowsiness, and carries on after the first sleep spindles where responses can still be observed. Hori and collaborators showed that a clear linear relationship exists between their 9 EEG stages and the slowing of reaction times, validating the rel-

evance of their graphoelements based classifications in describing the sleep onset period.

In parallel to this slowing, responses become progressively intermittent (Makeig et al., 1995; Ogilvie, 1989; Makeig et al., 2000). Subjects start to miss targets from sleep stage 1 (Ogilvie et al., 1989) and its associated EEG spectral power changes described above: delta, theta bands and sigma power increases (Makeig et al., 1995; Oken et al., 2006). Moreover, performances in more complex tasks (e.g. deviation from baseline in video games) are less and less accurate (Makeig et al., 2000).

What is responsible for this gradual loss of responsiveness to external events? Are responses already limited at early stages by a decreased ability of environmental stimuli perception? Or are the following steps of response production, i.e. ability to decide, ability to program and produce a response, impaired? The truth probably resides in between, with a progressive impairment of each step of cognitive processing while falling asleep.

Thereby, environmental stimuli perception seems gradually impaired at sleep onset. For instance, a decrease in sensory thresholds along sleep stages progression has been early documented (Bonnet et al., 1986). The thalamic deactivation at sleep onset has been involved in a progressive reduction of external information's transmission to the cortex, leading to a decreased perception of the environment. Studies on the P300 provide interesting information on that issue (Harsh et al., 1994, Cote et al., 2002). The P300, evoked by a deviant stimulus embedded in a train of standard, decreases as the sleep onset period progress and responsiveness to stimuli decreases. Moreover, its amplitude is related to the success in target detection. For instance, Cote et al. (2002) observed that during sleep stage 1 the P300 was absent when subjects failed to detect the target, and present even if attenuated at frontal sites when they were responding to the target. Behavioural responses were thus linked to the presence or absence of this change detection neural signature. This result points out a gradual disappearance of change detection systems at sleep onset.

Higher cognitive processes (decision making, motor planning…) are probably also impaired at sleep onset, involving a gradual loss of the capability to respond. This would be coherent with the reduced brain activity in structures involved in cognitive performances and action preparation (prefrontal cortex, locus coeruleus…) (Usher et al., 1999; Kaufman et al., 2006; Magnin et al., 2010). However, studies combining behavioural measures and imaging methods during the sleep onset period still lack to document this issue. Nonetheless, sleep deprivation studies combining PET and behavioural assessment already suggested a tight link between sleep propensity, decreased activity in thalamic and cortical areas (prefrontal and parietal), and reduced alertness and cognitive performances (Thomas et al., 2000). Conducting studies of this kind during the sleep onset period may be the key to disentangle the progressive disengagement of the different levels of cognitive processing at sleep onset.

Phenomenology of falling asleep

In parallel to the extensively studied physiological and behavioural modifications, one's phenomenology is dramatically modified while falling asleep. Although in every day's life, one's subjective feeling is the main criterion for wakefulness judgement, sleep onset period phenomenology, apart from the very famous hypnagogic phenomenon, received relatively little scientific attention. The behavioural attitude (eyes closed, lying down, retreat into oneself…) and physiological transition into a different vigilance state impact on subject's mind. During the falling asleep process, subjects pass through successive intermediate conscious states.

In a pioneer study associating polysomnography (PSG) and subjective reports, Foulkes and Vogel (1965) asked the participants "What were you experiencing just before I called you?", while they were falling asleep. Further questions allowed the investigation of the perceived state of vigilance and the quality and characteristics of their phenomenological experience. 212 reports collected at different junctures of the sleep onset period showed that physiological (eye movements patterns) and neurophysiological (alpha rhythm propensity) changes observed at sleep onset were paralleled by phenomenological modifications. With the progression towards sleep, subject's reports became higher in fantasy, while voluntary control of thoughts was decreasing.

A handful of studies based on a combination between prompted (generally by an auditory cue)

subjects reports and PSG recordings followed this first attempt to characterize sleep onset period phenomenology (Gibson et al., 1982; Hori et al., 1994; Lehmann et al., 1995; Tanaka et al., 1997; Wackermann et al., 2002; Yang et al., 2010), permitting now the integration of the psychological findings, physiological and behavioural data.

Hypnagogic Imagery

Probably the most striking phenomenological feature of SO is the emergence of hypnagogic imagery. These dreamlike hallucinations are symptomatic of the falling asleep period to such an extent that authors often refer to SO as the hypnagogic period.
Dreamlike mentation can be reported even before the classical onset of sleep stage I, and until a few minutes after the onset of sleep stage II (Foulkes and Vogel, 1965; Hori, 1985; 1982; 1994). Hori classification permits a better survey of hypnagogic activity in time: the percentage of hypnagogic reports is closely related to the 9 Hori sleep stages. This relationship is a U-shape function with a peak at H5 (Hori, 1994).
Hypnagogic imagery is often compared to dream imagery. These two phenomenon share various common features, like the presence of the different sensory modalities, the intrusive character of images (uncontrolled irruption into consciousness stream), their bizarreness, the abundance of symbols (Schacter, 1976)… Like dreams, hypnagogic images are mostly visuals. Auditory sensations are also present to a lesser extent (noises, music, speech…), as well as kinaesthetic feelings (falling sensations…) (Foulkes and Vogel, 1965; Schacter, 1976; Hori, 1994).
As we previously discussed, during the hypnagogic period the thalamo-cortical network is progressively deactivated. Moreover, there is a decoupling between thalamic and cortical deactivations (Magnin et al., 2010). This neurophysiological pattern (partial cortical activation and thalamic deactivation) could favour the development of hallucinatory images due to isolation of the brain from the environment and an alteration of cortical functionality, in a similar way that during REM sleep, dreams would be facilitated by a cortical reactivation despite preserved thalamic blockade.
Certain cortical regions, notably primary and secondary sensory areas (occipital visual areas, temporal auditory areas), remain active during the sleep onset period. Moreover, Hofle et al. (1997) showed that delta activity, which diminishes from frontal to posterior areas, is positively correlated with rCBF in visual and auditory cortices. Thus, delta activity development in various cortical areas could correspond to the emergence of sensory images.
Furthermore, the sensory modalities presented in hypnagogic imagery follow a sequential pattern that seems coherent with neurophysiological data. Thereby, while kinaesthetic images peak in H1, visual images are maximally reported in H5 or H6 (Hori 1994; Germain and Nielsen, 2001). Germain and Nielsen (2001) also showed that kinaesthetic images are associated with frontal delta power, and visual images with left central and temporal delta activity. These data suggest a strong association between delta expansion from frontal to posterior regions, and temporal hypnagogic imagery sensory features.

Loss of external world awareness

In parallel to hypnagogic imagery, subjects while falling asleep report a gradual loss of awareness of their surrounding environment. This effect is exhibited early in the sleep onset period, from the apparition of SEMs, and ends with a total loss of external world awareness after immersion in sleep stage 2 (Foulkes and Vogel, 1965; Gibson et al., 1982; Wackermann et al., 2002; Yang et al., 2010).
This decrease of environmental awareness obviously relates to the loss of responsiveness observed at the behavioural level (see above), and probably reinforces the immersion into hypnagogic images. It could result from the decreased thalamic activity at sleep onset (Hofle et al., 1997; Kaufman et al., 2006).

Disappearing control of thoughts

While progressing towards sleep, subjects also report a gradual loss of control over their thoughts. The appearance of hypnagogic images seems spontaneous, the coherence, temporal continuity and logic of thoughts are altered. This deterioration process is already present early in the sleep onset period (from the first SEMs) but dramatically increases with the first sleep spindles (Yang, 2010).
Various neurophysiological variables could be related to this cognitive impairment, for instance the decrease observed in the orbito-frontal cortex at the entrance in sleep stage II (Maquet, 1997; Hofle et al., 1997; Kaufman et al., 2006).

Loss of reality orientation and of time perception

In addition a loss of "reality-orientation" or ability to distinguish internally generated images from external perceptions is observed with the progression towards sleep (Foulkes and Vogel, 1965; Yang et al., 2010). Time perception seems also impaired. Indeed, subjects falling asleep are poor at estimating sleep latencies, or the time elapsed between two interactions with the experimenter (Gibson et al., 1982; Ogilvie 2001; Wackermann et al., 2002). These two phenomena, also characteristic of dreams, could be a result of the combination between loss of external awareness and disappearing control of thoughts at sleep onset.

Sleep perception

It is commonly admitted that a consistent perception of sleep is found only a few minutes after classical sleep stage II onset (Davis et al., 1937; Schacter, 1976; Ogilvie 2001; Yang et al., 2010). Before that final breakdown of vigilance, sleepiness and asleep/awake self reports increase gradually as the sleep onset period progresses (Oken et al., 2006; Wackermann et al., 2002; Hori et al., 1994; Yang et al., 2010). For instance, a close relationship exists between asleep/awake reports and the 9 Hori EEG stages (Hori et al., 1994).

But on which subjective basis are people judging that they are asleep or not? Which characteristics of their phenomenological experience do they use? Various characteristics of the sleep onset period phenomenology have been involved in sleep perception. For instance, Gibson et al. (1982) showed that correct subjective estimations of sleep stages correlated mainly with three phenomenological variables: external awareness, temporal awareness and the control over thoughts… According to a recent study by Yang et al. (2010), the loss of control over thinking processes would be the determinant subjective variable for sleep perception.

Discussion

How do we fall asleep? How do we regain consciousness? These are central questions to the understanding of consciousness and nevertheless bare attempts have been done to address them in depth from a cognitive point of view. Several studies have been done on drowsiness (Makeig et al., 1996; Huang et al., 2009; Kar et al., 2010) due to the importance of preventing traffic and work-related accidents. These studies look primarily at the errors made by participants but do not frame the results in key questions for the study of consciousness: When do we lose the capacity to consciously respond? When do we lose the capacity to consciously take a decision? Which sleep elements predict the changes in cognitive processes during the transition?

The first line of enquiries about transitions was started by Hori and collaborators and continued by Ogilvie et al. in the 80'. Both teams recognised the lack of detail in determining the transitions and tried to characterise sleep onset with different EEG and behavioural measures. The definition of the sleep EEG graphoelements every 5 seconds instead of 30 seconds (Hori et al., 1994) in the transition from wake to sleep broke with the classic assumption of the sleep medicine establishment that the conscious state is stationary during those 30 seconds (Retchaffen and Kale, 1968). This paved the way for more research challenging the criterion for wakefulness (and the loss of wakefulness). Ogilvie stated in the 1988 and 1989 that "if the criterion for wakefulness is cognitive response to external stimulation, only in EEG Stages 3, 4, and REM can accurate distinctions between sleep and wakefulness be made. If EEG is the criterion, then the data suggest that cognitive response is possible during Stages 1 and 2 sleep". They equated motor response to simple tones to being awake and found that the probability of response dramatically decreased from stage 1 to stage 2 and became close to zero in stage 3 (and 4). We have now advanced in defining what a conscious response is, or maybe it would be more accurate to say we have moved the boundary of unconscious responses to even inhibition of a response (van Gaal et al., 2008; Hughes et al., 2009; Boy et al., 2010).

Under the current frameworks for the study of consciousness a few criteria must be met for a response to qualify as conscious awareness movement. The problem underlying the definition of what constitutes a conscious response, arising from a conscious decision, comes from recent shift in the paradigm of volition and awareness (Baars and Gage, 2007). In the last decade there has been a myriad of investigations showing motor responses without awareness of the decision (Dijksterhuis and Aarts, 2010) and furthermore actions may be initiated even though we remain

unconscious of the goals or motivation of our behaviour (Custer and Aarts, 2010). This line of thought has moved the awareness line from action – a movement in response to stimuli is performed – to intention – a brain process causing the action –, and finally to goal – a brain process guided by belief that sets up the intentions. This theoretical framework does not take into account those mental processes occurring while consciousness fades into unconsciousness and therefore they are difficult to frame. Moreover, the batch of behavioural experiments performed during the transition is too modest to even start to fit them in these models. It might be better to think the future experiments in line with these complex accounts of consciousness keeping in mind the limited cognitive capacity of the people when they enter drowsiness.

Another avenue to explore when thinking about transitions is to keep the concept of awareness at its core (Dehaene and Naccache, 2001) by assuming that we are dealing with perceptual awareness. This simplifies the problem and allows us to experimentally test whether specific ERP or fMRI signatures at different points in the transition do show parieto-frontal activity causing top-down amplification (Dehaene et al., 2006). These specific neural signatures, if not too affected by the arousal changes, should help in the interpretation as to when a response (brain response or movement) is conscious, preconscious or unconscious. Maybe a complementary model is that one that does not rely on the ability to respond or purposeful behaviour as such but on a particular mode of information integration (Tononi, 2004). This framework relies in two conditions needed to attain consciousness; first, to what extent different regions of the thalamocortical system can interact causally (integration), and second, whether they can produce specific responses (information). The authors have been refining the theory and what and how to measure to further develop these ideas and make them suitable to be tested by a variety of methods and paradigms (see this volume).

The way forward to test the limits of conscious processing during the transition

Our proposal to study the transitions of consciousness, both in sleep or sedation studies, includes behavioral, electrophysiological and brain imaging measures with and without stimulation and instructions. This multifaceted approach will allow the fields of sleep, sedation and consciousness to have a common ground. The transitional approach, continuous testing of behaviour and neurophysiology during the transitions, aims at integrating the behavioural measures and neuromarkers of the cognitive sciences (perception, awareness, attention) with the physiological and brain markers of wakefulness.

In an archetypical experiment under this experimental framework the normal transition from wakefulness to SWS would be followed by high density EEG or EEG-fMRI, plus a series of physiological markers such as EMG, ECG and respiration rate (to complete the polysomnography). The participant would be assigned to an active or passive task; if active it may be from a range of executive functions tests going from a simple detection task to a stop signal task or a crossmodal judgement task. The inclusion of a parametric experimental design on the wake-sleep transition is a novel conceptual advance in the theoretical treatment of the axis of consciousness, wakefulness and awareness that should help move the field forward. Moreover, the perceptual and cognitive perturbations will allow a mapping of cognitive processes dynamics with behaviour, physiology and neurophysiology. The parsing of the data in single trial analysis with the combination of prestate/pretrial information, evoked responses and behavioural performance should permit to start answering key questions about transitions of consciousness (loss of the capacity of detection, discrimination, action, intention, goal, inhibition). Furthermore, the incorporation of integration measures in EEG and fMRI (coherence, local and global interactions, connectivity, causality, etc) will complete the picture by providing different accounts of the brain capacity before the stimulus (predictive of brain or muscle response), after the stimulus (as evoked neural markers of a cognitive process), and as covariates or regressors. Finally, the amalgamation of different accounts of sleep changes, neurophysiology of sedation and experimental theories of consciousness should become complementary in the quest for characterization of how consciousness fade, how it is regained, what are the different capacities of the brain during these changes and how can this impact on the clinical and social aspects of sleep and wakefulness.

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References

Acharya U.R., Faust O., Kannathal N., Chua T., Laxminarayan S. Non-linear analysis of EEG signals at various sleep stages. *Comput. Methods Programs Biomed.*, **80**: 37-45, 2005.

Andersson J.L., Onoe H., Hetta J., Lidstrom K., Valind S., Lilja A., Sundin A., Fasth K.J., Westerberg G., Broman J.E., Watanabe Y., Langstrom B. Brain networks affected by synchronized sleep visualized by positron emission tomography. *J. Cereb. Blood Flow Metab.*, **18**: 701-715, 1998.

Atienza M., Cantero J.L., Escera C. Auditory information processing during human sleep as revealed by event-related brain potentials. *Clin. Neurophysiol.*, **112**: 2031-2045, 2001.

Atienza M., Cantero J.L., Dominguez-Marin E. Mismatch negativity (MMN): an objective measure of sensory memory and long-lasting memories during sleep. *Int. J. Psychophysiol.*, **46**: 215-225, 2002.

Baars B. and Gage N. *Cognition, Brain and Consciousness.* London, Elsevier/Academic Press, 2007.

Baharav A., Kotagal S., Gibbons V., Rubin B.K., Pratt G., Karin J., Akselrod S. Fluctuations in autonomic nervous activity during sleep displayed by power spectrum analysis of heart rate variability. *Neurology*, **45**: 1183-1187, 1995.

Berger H. *Psyche.* Jena, Gustav Fischer, 1940.

Bonnet M.H. Auditory thresholds during continuing sleep. *Biol. Psychol.*, **22**: 3-10, 1986.

Borbely A.A. A two process model of sleep regulation. *Hum. Neurobiol.*, **1**: 195-204, 1982.

Borbély A.A., Achermann P., Meir H.K., Thomas R., William C.D. Sleep Homeostasis and Models of Sleep Regulation. In: *Principles and Practice of Sleep Medicine (Fourth Edition).* Philadelphia, PA, W.B. Saunders: 405-417, 2005.

Boy F., Husain M., Singh K.D., Sumner P. Supplementary motor area activations in unconscious inhibition of voluntary action. *Exp. Brain Res.*, **206**: 441-448, 2010.

Brugge J.F. and Merzenich M.M. Responses of neurons in auditory cortex of the macaque monkey to monaural and binaural stimulation. *J. Neurophysiol.*, **36**: 1138-1158, 1973.

Cantero J.L., Atienza M., Salas R.M., Gomez C.M. Alpha EEG coherence in different brain states: an electrophysiological index of the arousal level in human subjects. *Neurosci. Lett.*, **271**: 167-170, 1999.

Cote K.A., De Lugt D.R., Campbell K.B. Changes in the scalp topography of event-related potentials and behavioral responses during the sleep onset period. *Psychophysiology*, **39**: 29-37, 2002.

Custers R. and Aarts H. The unconscious will: how the pursuit of goals operates outside of conscious awareness. *Science*, **329**: 47-50, 2010.

Czisch M., Wehrle R., Kaufmann C., Wetter T.C., Holsboer F., Pollmacher T., Auer D.P. Functional MRI during sleep: BOLD signal decreases and their electrophysiological correlates. *Eur. J. Neurosci.*, **20**: 566-574, 2004.

Danker-Hopfe H., Anderer P., Zeitlhofer J., Boeck M., Dorn H., Gruber G., Heller E., Loretz E., Moser D., Parapatics S., Saletu B., Schmidt A., Dorffner G. Interrater reliability for sleep scoring according to the Rechtschaffen & Kales and the new AASM standard. *J. Sleep Res.*, **18**: 74-84, 2009.

Davis H., Davis P.A., Loomis A.L., Harvey E.N., Hobart G. Changes in Human Brain Potentials During the Onset of Sleep *Science*, **86**: 448-450, 1937.

De Gennaro L., Ferrara M., Ferlazzo F., Bertini M. Slow eye movements and EEG power spectra during wake-sleep transition. *Clin. Neurophysiol.*, **111**: 2107-2115, 2000.

De Gennaro L. and Ferrara M. Sleep spindles: an overview. *Sleep Med. Rev.*, **7**: 423-440, 2003.

De Lugt D.R., Loewy D.H., Campbell K.B. The effect of sleep onset on event related potentials with rapid rates of stimulus presentation. *Electroencephalogr. Clin. Neurophysiol.*, **98**: 484-492, 1996.

Dehaene S. and Naccache L. Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. *Cognition*, **79**: 1-37, 2001.

Dehaene S., Changeux J.P., Naccache L., Sackur J., Sergent C. Conscious, preconscious, and subliminal processing: a testable taxonomy. *Trends Cogn. Sci.*, **10**: 204-211, 2006.

Dijksterhuis A. and Aarts H. Goals, attention, and (un)consciousness. *Annu. Rev. Psychol.*, **61**: 467-490, 2010.

Dvornyk V., Vinogradova O., Nevo E. Origin and evolution of circadian clock genes in prokaryotes. *Proc. Natl. Acad. Sci. U S A*, **100**: 2495-2500, 2003.

Edeline J.M., Manunta Y., Hennevin E. Auditory thalamus neurons during sleep: changes in frequency selectivity, threshold, and receptive field size. *J. Neurophysiol.*, **84**: 934-952, 2000.

Foulkes D. and Vogel G. Mental Activity at Sleep Onset. *J. Abnorm. Psychol.*, **70**: 231-243, 1965.

Germain A. and Nielsen T.A. EEG Power Associated with Early Sleep Onset Images Differing in Sensory Content. *Sleep Res. Online*, **4**: 83-90, 2001.

Gibson E., Perry F., Redington D., Kamiya J. Discrimination of sleep onset stages: behavioral responses and verbal reports. *Percept. Mot. Skills*, **55**: 1023-1037, 1982.

Harsh J., Voss U., Hull J., Schrepfer S., Badia P. ERP and behavioral changes during the wake/sleep transition. *Psychophysiology*, **31**: 244-252, 1994.

Hofle N., Paus T., Reutens D., Fiset P., Gotman J., Evans A.C., Jones B.E. Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans. *J. Neurosci.*, **17**: 4800-4808, 1997.

Hori T. Electrodermal and Electro-oculographic Activity in a Hypnagogic State. *Psychophysiology*, **19**: 668-672, 1982.

Hori T. Spatiotemporal changes of EEG activity during waking-sleeping transition period. *Int. J. Neurosci.*, **27**: 101-114, 1985.

Hori T., Hayashi M., Morikawa T. Topographical EEG changes and the hypnagogic experience. pp. 237-253. In: Ogilvie R.D. and Harsh J.R. (Eds.). *Sleep Onset: Normal and Abnormal Processes.* Washington DC, American Psychological Association, 1994.

Huang R.S., Jung T.P., Makeig S. Tonic Changes in EEG Power Spectra during Simulated Driving. San Diego, USA, Proceedings of the 5th International Conference on Foundations of Augmented Cognition, Springer-Verlag, 2009.

Hughes G., Velmans M., De Fockert J. Unconscious priming of a no-go response. *Psychophysiology*, **46**: 1258-1269, 2009.

Issa E.B. and Wang X. Sensory responses during sleep in primate primary and secondary auditory cortex. *J. Neurosci.*, **28**: 14467-14480, 2008.

Kajimura N., Uchiyama M., Takayama Y., Uchida S., Uema T., Kato M., Sekimoto M., Watanabe T., Nakajima T., Horikoshi S., Ogawa K., Nishikawa M., Hiroki M., Kudo Y., Matsuda H., Okawa M., Takahashi K. Activity of midbrain reticular formation and neocortex during the progression of human non-rapid eye movement sleep. *J. Neurosci.*, **19**: 10065-10073, 1999.

Kar S., Routray A., Nayak B.P. Functional network changes associated with sleep deprivation and fatigue during simulated driving: Validation using blood biomarkers. *Clin. Neurophysiol.*, 2010.

Kaufmann C., Wehrle R., Wetter T.C., Holsboer F., Auer D.P., Pollmacher T., Czisch M. Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: an EEG/fMRI study. *Brain*, **129**: 655-667, 2006.

Kjaer T.W., Law I., Wiltschiotz G., Paulson O.B., Madsen P.L. Regional cerebral blood flow during light sleep--a H(2)(15)O-PET study. *J. Sleep Res.*, **11**: 201-207, 2002.

Laufs H., Walker M.C., Lund T.E. "Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: an EEG/fMRI study" – its limitations and an alternative approach. *Brain*, **130**: 75-76, 2007.

Lehmann D., Grass P., Meier B. Spontaneous conscious covert cognition states and brain electric spectral states in canonical correlations. *Int. J. Psychophysiol.*, **19**: 41-52, 1995.

Magnin M., Rey M., Bastuji H., Guillemant P., Mauguiere F., Garcia-Larrea L. Thalamic deactivation at sleep onset precedes that of the cerebral cortex in humans. In: *Proceedings of the National Academy of Sciences*, 2010.

Magosso E., Ursino M., Provini F., Montagna P. Wavelet analysis of electroencephalographic and electro-oculographic changes during the sleep onset period. In: *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2007.

Makeig S. and Jung T.P. Changes in alertness are a principal component of variance in the EEG spectrum. *Neuroreport*, **7**: 213-216, 1995.

Makeig S. and Jung T.P. Tonic, phasic, and transient EEG correlates of auditory awareness in drowsiness. *Brain Res. Cogn. Brain Res.*, **4**: 15-25, 1996.

Makeig S., Jung T.P., Sejnowski T.J. Awareness during drowsiness: dynamics and electrophysiological correlates. *Can. J. Exp. Psychol.*, **54**: 266-273, 2000.

Maquet P., Dive D., Salmon E., Sadzot B., Franco G., Poirrier R., Franck G. Cerebral glucose utilization during stage 2 sleep in man. *Brain Res.*, **571**: 149-153, 1992.

Maquet P., Degueldre C., Delfiore G., Aerts J., Peters J.M., Luxen A., Franck G. Functional neuroanatomy of human slow wave sleep. *J. Neurosci.*, **17**: 2807-2812, 1997.

Massimini M., Ferrarelli F., Huber R., Esser S.K., Singh H., Tononi G. Breakdown of cortical effective connectivity during sleep. *Science*, **309**: 2228-2232, 2005.

Massimini M., Boly M., Casali A., Rosanova M., Tononi G. A perturbational approach for evaluating the brain's capacity for consciousness. *Prog. Brain Res.*, **177**: 201-214, 2009.

Murata K. and Kameda K. The Activity of Single Cortical Neurones of Unrestrained Cats During Sleep and Wakefulness. *Arch. Ital. Biol.*, **101**: 306-331, 1963.

Nittono H., Momose D., Hori T. The vanishing point of the mismatch negativity at sleep onset. *Clin Neurophysiol*, **112**: 732-739, 2001.

Noldy N., McGarry P., Campbell K. Late auditory evoked potentials as indicators of sleep onset. In: W K., Obal F., H S., Visser P. (Eds.). *Sleep '86.* Stuttgart, Pontenegal Press: 277-280, 1988.

Ogilvie R.D., Wilkinson R.T., Allison S. The detection of sleep onset: behavioral, physiological, and subjective convergence. *Sleep*, **12**: 458-474, 1989.

Ogilvie R.D. The process of falling asleep. *Sleep Med. Rev.*, **5**: 247-270, 2001.

Oken B.S., Salinsky M.C., Elsas S.M. Vigilance, alertness, or sustained attention: physiological basis and measurement. *Clin. Neurophysiol.*, **117**: 1885-1901, 2006.

Ornitz E.M., Ritvo E.R., Carr E.M., La Franchi S., Walter R.D. The effect of sleep onset on the auditory averaged evoked response. *Electroencephalogr. Clin. Neurophysiol.*, **23**: 335-341, 1967.

Pace-Schott E.F. and Hobson J.A. The Neurobiology of Sleep: Genetics, cellular physiology and subcortical networks. *Nat. Rev. Neurosci.*, **3**: 591-605, 2002.

Pelayo R. and Guilleminault C. History of Sleep Research. In: Stickgold R., Walker M.P. (Eds.). *The neuroscience of sleep.* Amsterdam, Boston, Academic Press/Elsevier: 3-6, 2009.

Peña J.L., Perez-Perera L., Bouvier M., Velluti R.A. Sleep and wakefulness modulation of the neuronal firing in the auditory cortex of the guinea pig. *Brain Res.*, **816**: 463-470, 1999.

Pivik R.T. and Busby K. Heart rate associated with sleep onset in preadolescents. *J. Sleep Res.*, **5**: 33-36, 1996.

Portas C.M., Krakow K., Allen P., Josephs O., Armony J.L., Frith C.D. Auditory processing across the sleep-wake cycle: simultaneous EEG and fMRI monitoring in humans. *Neuron.*, **28**: 991-999, 2000.

Rechtschaffen A. and Kale A. A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects. U.S. Govt Printing Office, Washington DC, 1968.

Ruby P., Caclin A., Boulet S., Delpuech C., Morlet D. Odd sound processing in the sleeping brain. *J. Cogn. Neurosci.*, **20**: 296-311, 2008.

Sabri M., Labelle S., Gosselin A., Campbell K.B. Effects of sleep onset on the mismatch negativity (MMN) to frequency deviants using a rapid rate of presentation. *Brain Res. Cogn. Brain Res.*, **17**: 164-176, 2003.

Schabus M., Dang-Vu T.T., Albouy G., Balteau E., Boly M., Carrier J., Darsaud A., Degueldre C., Desseilles M., Gais S., Phillips C., Rauchs G., Schnakers C., Sterpenich V., Vandewalle G., Luxen A., Maquet P. Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. *Proc. Natl. Acad. Sci. U S A*, **104**: 13164-13169, 2007.

Schacter D.L. The hypnagogic state: a critical review of the literature. *Psychol. Bull.*, **83**: 452-481, 1976.

Schwartz W.J. Circadian oscillations in the suprachiasmatic nucleus. In: Squire L.R. (Ed.). *Encyclopedia of Neuroscience.* Oxford, Academic Press: 939-944, 2009.

Shen Y., Olbrich E., Achermann P., Meier P.F. Dimensional complexity and spectral properties of the human sleep EEG. Electroencephalograms. *Clin. Neurophysiol.*, **114**: 199-209, 2003.

Silber M.H., Ancoli-Israel S., Bonnet M.H., Chokroverty S., Grigg-Damberger M.M., Hirshkowitz M., Kapen S., Keenan S.A., Kryger M.H., Penzel T., Pressman M.R., Iber C. The visual scoring of sleep in adults. *J. Clin. Sleep Med.*, **3**: 121-131, 2007.

Spoormaker V.I., Schroter M.S., Gleiser P.M., Andrade K.C., Dresler M., Wehrle R., Samann P.G., Czisch M. Development of a large-scale functional brain network during human non-rapid eye movement sleep. *J. Neurosci.*, **30**: 11379-11387, 2010.

Steriade M., Contreras D., Curro Dossi R., Nunez A. The slow (< 1 Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting thalamic and neocortical networks. *J. Neurosci.*, **13**: 3284-3299, 1993.

Steriade M. and McCarley W. *Brain Control of Wakefulness and Sleep* New York, Kluwer Academic, 2005.

Susmakova K. Correlation Dimension versus Fractal Exponent During Sleep Onset. *Measurement Sci. Rev.*, **6**: 58-64, 2006.

Susmakova K. and Krakovska A. Discrimination ability of individual measures used in sleep stages classification. *Artif. Intell. Med.*, **44**: 261-277, 2008.

Tanaka H., Hayashi M., Hori T. Statistical features of hypnagogic EEG measured by a new scoring system. *Sleep*, **19**: 731-738, 1996.

Tanaka H., Hayashi M., Hori T. Topographical characteristics and principal component structure of the hypnagogic EEG. *Sleep*, **20**: 523-534, 1997.

Tanaka H., Hayashi M., Hori T. Topographic mapping of electroencephalography coherence in hypnagogic state. *Psychiatry Clin. Neurosci.*, **52**: 147-148, 1998.

Tanaka H., Hayashi M., Hori T. Topographic mapping of EEG spectral power and coherence in delta activity during the transition from wakefulness to sleep. *Psychiatry Clin. Neurosci.*, **53**: 155-157, 1999.

Thomas M., Sing H., Belenky G., Holcomb H., Mayberg H., Dannals R., Wagner H., Thorne D., Popp K., Rowland L., Welsh A., Balwinski S., Redmond D. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J. Sleep Res.*, **9**: 335-352, 2000.

Tononi G. An information integration theory of consciousness. *BMC Neurosci.*, **5**: 42, 2004.

Usher M., Cohen J.D., Servan-Schreiber D., Rajkowski J., Aston-Jones G. The role of locus coeruleus in the regulation of cognitive performance. *Science*, **283**: 549-554, 1999.

Van den Heuvel C.J., Noone J.T., Lushington K., Dawson D. Changes in sleepiness and body temperature precede nocturnal sleep onset: evidence from a polysomnographic study in young men. *J. Sleep Res.*, **7**: 159-166, 1998.

Van Gaal S., Ridderinkhof K.R., Fahrenfort J.J., Scholte H.S., Lamme V.A. Frontal cortex mediates unconsciously triggered inhibitory control. *J. Neurosci.*, **28**: 8053-8062, 2008.

Vyazovskiy V.V.,Olcese U., Hanlon E.C., Nir Y., Cirelli C., Tononi G. Local sleep in awake rats. *Nature*, **472**: 443–447, 2011.

Wackermann J., Putz P., Buchi S., Strauch I., Lehmann D. Brain electrical activity and subjective experience during altered states of consciousness: ganzfeld and hypnagogic states. *Int. J. Psychophysiol.*, **46**: 123-146, 2002.

Worsnop C., Kay A., Pierce R., Kim Y., Trinder J. Activity of respiratory pump and upper airway muscles during sleep onset. *J. Appl. Physiol.*, **85**: 908-920, 1998.

Yang C.M., Han H.Y., Yang M.H., Su W.C., Lane T. What subjective experiences determine the perception of falling asleep during sleep onset period? *Conscious. Cogn.*, **19**: 1084-1092, 2010.

Zimmerman J.E., Naidoo N., Raizen D.M., Pack A.I. Conservation of sleep: insights from non-mammalian model systems. *Trends Neurosci.*, **31**: 371-376, 2008.