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CHAPTER 8

Spontaneous neural activity during human non-rapid eye movement sleep

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Abstract: Recent neuroimaging studies characterized the neural correlates of slow waves and spindles during human non-rapid eye movement (NREM) sleep. They showed that significant activity was consistently associated with slow (>140 μV) and delta waves (75–140 μV) during NREM sleep in several cortical areas including inferior frontal, medial prefrontal, precuneus, and posterior cingulate cortices. Unexpectedly, slow waves were also associated with transient responses in the pontine tegmentum and in the cerebellum. On the other hand, spindles were associated with a transient activity in the thalami, paralimbic areas (anterior cingulate and insular cortices), and superior temporal gyri. Moreover, slow spindles (11–13 Hz) were associated with increased activity in the superior frontal gyrus. In contrast, fast spindles (13–15 Hz) recruited a set of cortical regions involved in sensorimotor processing, as well as the mesial frontal cortex and hippocampus.

These findings indicate that human NREM sleep is an active state during which brain activity is temporally organized by spontaneous oscillations (spindles and slow oscillation) in a regionally specific manner. The functional significance of these NREM sleep oscillations is currently interpreted in terms of synaptic homeostasis and memory consolidation.

Keywords: NREM sleep; slow waves; spindles; EEG/fMRI.

Introduction

Brain glucose and oxygen metabolism and cerebral blood flow are known to decrease during non-rapid eye movement (NREM) sleep, relative to waking levels (Maquet, 1995, 2000). This decrease parallels the decrease in average neural firing rates during NREM sleep, relative to waking levels (Vyazovskiy et al., 2009). However, during NREM sleep, a critical aspect of brain activity consists of the adoption of bursting firing patterns in large neuronal populations, resulting in the emergence of typical oscillations on electroencephalographic (EEG)

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recordings, that is, spindles and slow waves. Because these oscillations have been implied in central sleep functions, such as information processing or sleep homeostasis, recent attempts have been made to characterize in greater details the neural correlates of NREM sleep oscillations, by resorting to advanced neuroimaging techniques, such as simultaneous EEG and functional magnetic resonance imaging (fMRI), high-density EEG, or magnetoencephalographic (MEG) recordings. In this chapter, we review recent advances in characterizing the neural correlates of human slow waves and spindles.

Slow waves

A slow rhythm (<1 Hz) constitutes the fundamental rhythm which characterizes NREM sleep. Originally, unit recordings in cats showed that the neuronal membrane potential oscillates at low frequency (around 1 Hz). This oscillation shapes neuronal activity, by alternating a depolarizing phase, associated with important neuronal firing (up-state), and a hyperpolarizing phase, during which cortical neurons remain silent for a few hundred milliseconds (down-state; Steriade et al., 1993b, 2001). During NREM sleep, this so-called slow oscillation (<1Hz) is recorded in all major types of neocortical neurons (both excitatory and inhibitory) and occurs synchronously in large neuronal populations. At the population level, the activity is therefore made up of the alternation of ON states and OFF states (Vyazovskiy et al., 2009). Because these events represent massive and synchronous changes in large neuronal populations, they can be reflected on EEG recordings as large amplitude low-frequency waves (Steriade et al., 1993a). The slow oscillation is generated by the cortex as it can be observed after thalamic destruction (Steriade et al., 1993a), in cortical slabs isolated from thalamic influence (Timofeev et al., 2000), or in cortical slices (Sanchez-Vives and McCormick, 2000). However, in the intact animal, the slow (<1 Hz) rhythm of NREM sleep is an "emergent property of cortico-thalamo-cortical networks", (Crunelli and Hughes, 2010).

In humans, the classification of NREM sleep slow waves is not always clear. A slow rhythm was initially identified on scalp EEG recordings as the recurrence of spindles (Achermann and Borbely, 1997) or their grouping by slow waves (Molle et al., 2002). More recently, high-amplitude slow waves themselves were taken as realization of the slow rhythm (Massimini et al., 2004). On the other hand, historically, the power density in the 0.75–4 Hz frequency band, usually referred to as "slow wave activity" (SWA), has proved a very useful and popular parameter because it quantifies the dissipation of homeostatic sleep pressure during NREM sleep (Borbely, 2001). The frequency bounds of SWA do not respect the dichotomy between slow (<1 Hz) and delta rhythms (1–4 Hz), which is based on differences in the respective cellular correlates of these rhythms in animals (Steriade and McCarley, 2005). In the temporal domain, the amplitude of SWS waves is classically larger than 75 μV (Rechtschaffen and Kales, 1968) but only the largest waves (>140 μV) were taken as realizations of the slow oscillation (<1 Hz; Massimini et al., 2004; Molle et al., 2002). This approach suggests that relatively smaller waves (amplitude between 75 and 140 μV) correspond to delta waves (1–4 Hz). These faster waves of smaller amplitude would also be an expression of the slow oscillation but would arise when the synchronization in the network is less marked (Esser et al., 2007; Vyazovskiy et al., 2009).

On scalp EEG recording, SWA predominates over frontal areas (Finelli et al., 2001), where indeed the largest waves are typically recorded. However, an analysis of individual waves demonstrated the spatial variability of slow waves. Each wave originates at a specific site and travels over the scalp following a particular trajectory (Massimini et al., 2004). Waves originate more frequently in frontal regions and travel backward to

posterior areas. Beyond this variability, slow waves seem to recruit systematically various brain regions. Early studies based on regional cerebral blood flow (rCBF) measurement by positron emission tomography (PET) reported that the power density of delta waves (1.5–4 Hz) during NREM sleep was negatively correlated with rCBF in the ventromedial prefrontal cortex, the basal forebrain, the striatum, the anterior insula, and the precuneus (Dang-Vu et al., 2005). Using simultaneous EEG and event-related fMRI, it was possible to show that slow waves were consistently associated with transient increases in regional blood oxygen level dependent (BOLD) signal (Dang-Vu et al., 2008). Slow waves were associated with significant increases in activity in the pontine tegmentum, the cerebellar hemispheres, right parahippocampal gyrus, bilateral inferior and medial frontal cortices, precuneus, and posterior cingulate cortex (Fig. 1). As compared to baseline activity, the largest waves (>140 μV) were associated with significant activity in the parahippocampal gyrus,

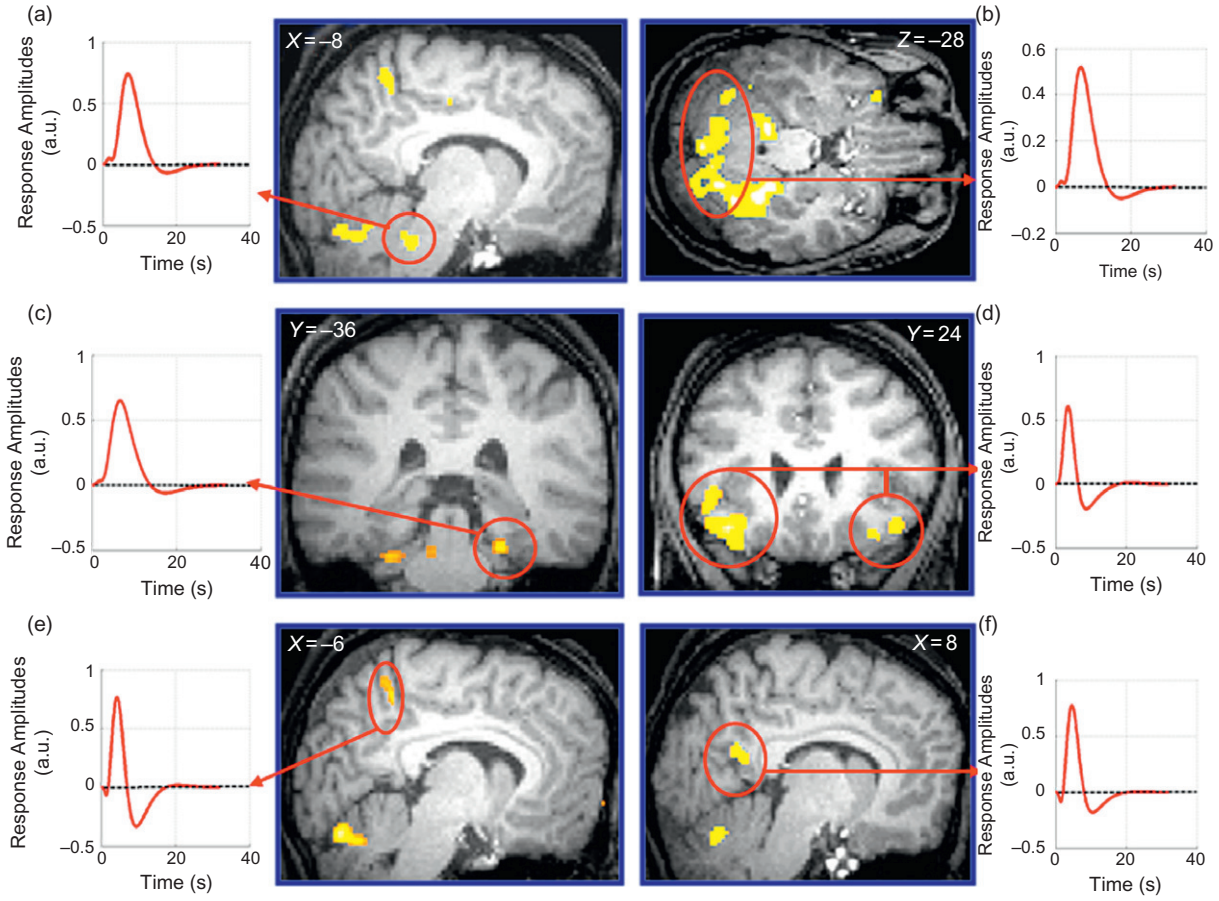

Fig. 1. Central panels: brain responses to NREM sleep slow waves. Side panels: time course (in seconds) of fitted response amplitudes (in arbitrary units) during slow oscillation in the corresponding circled brain area. All responses consisted in regional increases of brain activity. (a) Pontine tegmentum, (b) cerebellum, (c) right parahippocampal gyrus, (d) inferior frontal gyrus, (e) precuneus, (f) posterior cingulate cortex. Adapted from Dang-Vu et al. (2008).

cerebellum, and brainstem whereas delta waves were related to frontal responses.

Transient surges of activity in the brainstem, time-locked to scalp EEG slow waves was an unexpected finding, given that NREM sleep is associated with decreased average firing rate in many nuclear groups of the reticular formation (Steriade and McCarley, 2005). However, recent studies reported that neurons in the pedunculo-pontine nucleus (Mena-Segovia et al., 2008) and the locus coeruleus (Yeshenko et al., 2006) fire rhythmically during cortical slow oscillations. The functional consequences of this rhythmic activity are not yet characterized. However, assuming scalp EEG slow waves can be reliably mapped onto the alternation of ON and OFF states; it is tempting to suggest that ON states might correspond to microwake states, not only because of the high neural activity within the cortex (Destexhe et al., 2007) but also due to the potential restoration of neuromodulatory contexts similar to wakefulness, due to the associated pulsatile brainstem activity.

The cerebellar activity during NREM sleep has hardly been investigated. Early studies reported a decrease in firing rates in Purkinje cells during NREM sleep (Hobson and McCarley, 1972). It is still unknown whether firing is time-locked to cortical slow waves and further investigations should characterize the relations between cerebellar activity and corticothalamic oscillations.

The transient activity observed in frontal, parietal, and cingulate areas in relation to EEG slow waves suggest that they belong to their preferred propagation pathways. Indeed, these areas correspond to major structural connectivity nodes in the human brain (Hagmann et al., 2008; Honey et al., 2009). In addition, confirming fMRI results, source reconstruction of scalp high-density EEG recordings showed that spontaneous slow waves preferentially involve the precuneus, the posterior cingulate, ventro-lateral, and medial frontal areas, whereas they more frequently originate in the insula and cingulate gyrus (Murphy et al., 2009).

The parahippocampal gyrus is also a densely connected area of the human brain (Hagmann et al., 2008). Its activity associated with EEG slow waves might suggest that this region is also one of their preferred propagation pathways, possibly en route to or coming from the hippocampus. Alternatively, it was recently shown that the parahippocampal gyrus was a prominent site of initiation of gamma oscillations that are coupled with the fMRI BOLD signal (Nir et al., 2007), in synchrony with cortical slow waves (Le Van Quyen et al., 2010). The functional significance for this local parahippocampal activity is still unclear, although it might participate in the interplay between the hippocampus and the neocortex during NREM sleep (Buzsaki, 1996; Isomura et al., 2006).

In conclusion, beyond the variability in their individual trajectory, slow waves consistently recruit a distributed set of subcortical and cortical areas, which can be viewed as their common nodes of propagation. Moreover, slow waves are deemed faithfully reflecting the dissipation of local sleep pressure accrued during wakefulness (Borbely, 1982) potentially through a recalibration of glutamatergic neurotransmission (Tononi and Cirelli, 2003; Vyazovskiy et al., 2008, 2009). This assumption implies that brain areas consistently recruited by EEG slow waves are, on average, among the most active during wakefulness. Accordingly, ultraslow fluctuations of activity (< 0.1 Hz) are recorded using fMRI during wakefulness in many of the areas recruited by EEG slow waves during NREM sleep (Damoiseaux et al., 2006). In particular, the precuneus, posterior cingulate cortex, insula, and ventral frontal areas seem to shape perception of external stimuli by conveying contextual information (Sadaghiani et al., 2010) related, for instance, to predictions about future events (Fox and Raichle, 2007). In contrast, the status of brainstem and cerebellar structure in this respect remains to be determined.

Spindles

Spindles constitute the hallmark of light NREM sleep, although they can still be detected in lower amounts during deep NREM sleep. In humans,

spindles consist of waxing-and-waning 11–15 Hz oscillations, lasting 0.5–3 s. At the cellular level, spindles arise from cyclic inhibition of thalamocortical (TC) neurons by reticular thalamic (RT) neurons. Postinhibitory rebound spike bursts in TC cells entrain cortical populations in spindle oscillations (Steriade and McCarley, 2005). In addition, two kinds of spindles are described in humans. Slow spindles (grossly <13 Hz) predominate over frontal areas, whereas fast spindles (>13 Hz) prevail over centro-parietal areas. These two spindling activities differ by their circadian and homeostatic regulations, pharmacological reactivity, development in infancy, evolution during aging, modulation during menstrual cycle, and pregnancy (De Gennaro and Ferrara, 2003), and intriguingly, by their association with general cognitive capabilities (Bodizs et al., 2005) and memory processing (Schabus, 2009). Despite these functional differences, it is still debated whether slow and fast spindles reflect the activity of different neural networks or the differential modulation of a single generator.

Little is known about the cerebral correlates of human spindles. Scalp multichannel EEG recordings consistently reported the existence of two spindle types, although recent MEG data indicate the possibility of multiple spindle oscillators in the human brain (Dehghani et al., 2010). Based on EEG recording, slow spindles (centered around 12 Hz) exhibit a variable topography, primarily over the frontal cortex (Doran, 2003). In contrast, fast spindles (centered at 14 Hz) are topographically and dynamically limited to the superior central and parietal cortex (Doran, 2003). Source reconstruction of scalp EEG recordings identified two sources, one for slow spindles in a mesial frontal region and another for fast spindles in the precuneus (Anderer et al., 2001), a result confirmed by MEG magnetic source reconstruction (Manshanden et al., 2002). Early PET studies reported a negative relationship between thalamic cerebral blood flow and the power spectrum in the spindle frequency band (Hofle et al., 1997). Taking advantage of the better temporal resolution of EEG/fMRI, it was later shown that human spindles were also associated with transient surge in activity in the thalami, paralimbic areas (anterior cingulate and insular cortices), and superior temporal gyri (Fig. 2; Schabus et al., 2007). Slow spindles were further associated with increased activity in the superior frontal gyrus. In contrast, fast spindles recruited the mesial frontal cortex and hippocampus, as well as a set of cortical regions involved in sensorimotor processing: sensorimotor cortices, supplementary motor area, and midcingulate cortex. The recruitment of partially segregated cortical networks for slow and fast spindles further supports the existence of two spindle types during human NREM sleep, with potentially different functional significance.

For instance, the μ rhythm is a conspicuous spontaneous rhythm of relaxed wakefulness, involving the sensorimotor and premotor cortices (Hari and Salmelin, 1997). Intriguingly, although cortical generators of spindles involve a larger part of the cortex than μ rhythm (Manshanden et al., 2002), spindles and μ rhythm seem functionally related. Indeed, in cats, enhancement of sensorimotor rhythm through conditioning during wakefulness increases spindles and decreases motor output during subsequent sleep (Sterman et al., 1970). These findings suggest that the oscillatory properties of sensorimotor TC loops, shaped by NREM sleep oscillatory and neuromodulatory contexts, result in the generation in fast spindles.

More generally, fast spindles have been related to procedural and declarative memory consolidation during sleep (Schabus, 2009). Functional MRI results suggest that even without any previous training, fast relative to slow spindles are associated with high activity in thalamo-sensorimotor loops, a condition which could promote their functional interactions and participate in the processing of procedural motor learning. By the same token, the recruitment of mesial frontal and hippocampal structures by fast spindles suggests that these oscillations are associated with favorable conditions for hippocampal–frontal interactions, which are deemed important in the consolidation of declarative memories.

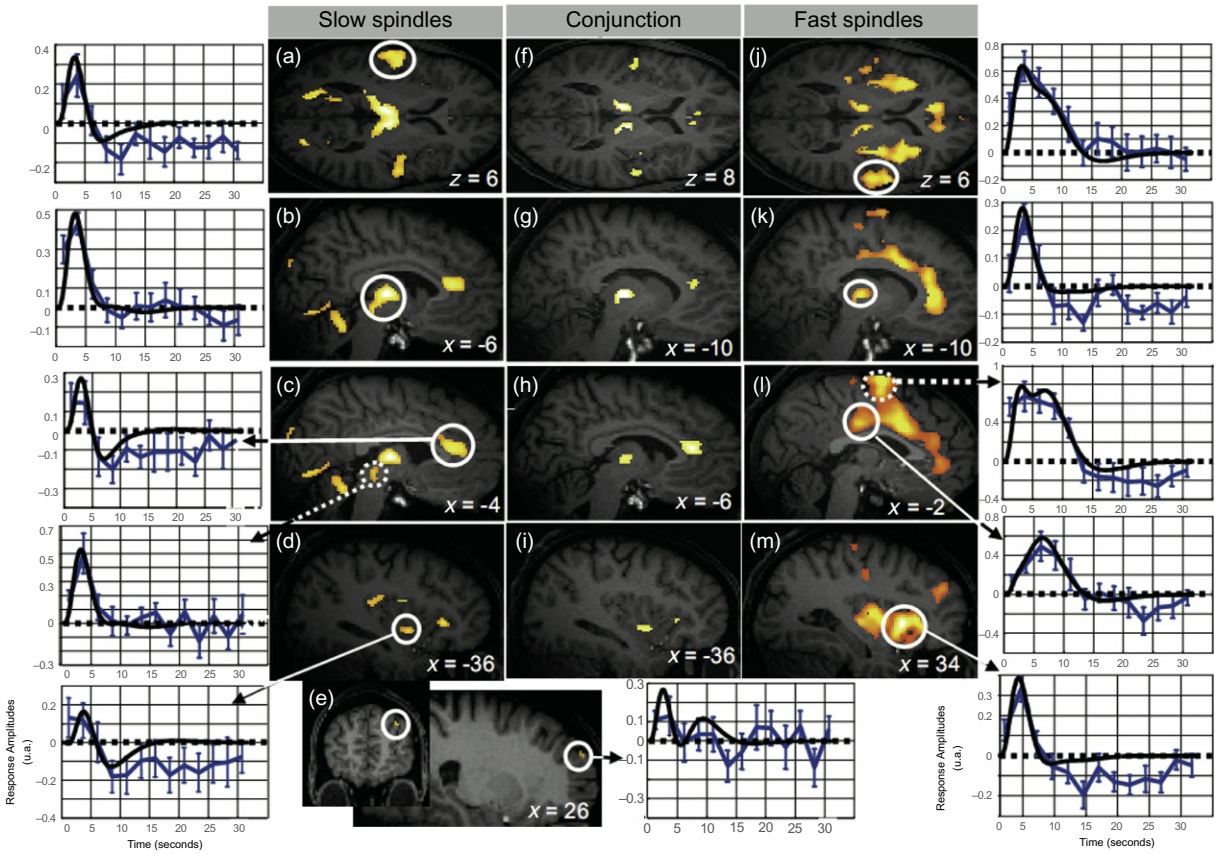

Fig. 2. Responses to spindles (blue; fitted responses in black). Left panels (a–e): fMRI responses to slow spindles. Leftmost panels: responses time course in (a) auditory cortices (circled), (b) thalamus, (c) anterior cingulate (circled) and midbrain tegmentum (dotted), as well as (d) anterior insula and (e) superior frontal gyrus (circled). Center panels (f–i): common response pattern to all spindles. Right panels (j–m): fMRI responses to fast spindles. Rightmost panels: response time course in (j) superior temporal gyri, (k) thalami, (l) midcingulate cortex (circled) and supplementary motor area (dotted), as well as (m) anterior insula. Adapted from Schabus et al. (2007).

Conclusions

NREM sleep oscillations are associated with the recruitment of consistent sets of brain areas. Future research should investigate how brain structural connectivity constrains the propagation of these oscillations and their functional significance for the maintenance of optimal waking brain function.

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