Patterns of functional connectivity in the human brain across the sleep-wake cycle

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Abstract
Searching the neural code underlying consciousness and cognition is one of the most important goals in contemporary neuroscience. Research with neuronal oscillations at the level of single-neuron, local cell assemblies, and network system have provided invaluable insights into different mechanisms of synaptic interactions involved in the emergence of cognitive acts. Recent advances on neural synchronization mechanisms potentially
involved in brain integration processes are discussed, emphasizing the value of scalp and intracranial EEG recordings at determining local- and large-scale dynamics in the human brain. This review blends results from different levels of analysis with the firm conviction that state-dependent brain dynamics at different levels of integration can provide a deeper understanding of neural correlates of consciousness and sleep functions.

1. Introduction

A broad range of methodological approaches in neuroscience has established that the brain is organized in multiple functional units at different spatio-temporal scales. It is commonly believed that cognition intimately depends on the functioning of the cerebral cortex. Thus, many important cortical functions result from the coordinated cooperation of different neuronal ensembles, and can be measured with recording techniques targeted at this level.

Oscillatory brain activity is a ubiquitous property of the nervous system in all species. Oscillations are often generated within a vast frequency range both by single neurons and large functional groups of neurons (assemblies). It is widely accepted, however, that the neural code is distributed in cell assemblies rather than encoded by firing rates of single cells [1, 2]. Although it is unknown how the neural code is integrated in spontaneous and evoked brain oscillations, synchrony has been largely viewed as a potential valid mechanism for cerebral integration [3, 4]. In fact, neurons extract more information from their inputs when they are synchronized, regardless of changes in their firing rates [5]. Growing evidence prompts the thought that different levels of cerebral integration mediated by various scales of spatial and temporal synchrony over multiple frequency bands could play a key functional role in the emergence of percepts, memories, emotions, thoughts, and actions [6, 7, 8].

Several controversial issues have impeded the drawing of definitive conclusions regarding the putative role of synchronic brain oscillations [9, 10, 11, 12]. The importance of neuroanatomical differences between species, mainly between lower mammals and humans, is usually neglected in determining electrophysiological properties of cerebral oscillations [13]. Likewise, neural synchrony in the human brain shows different patterns depending on spatial scales of measurement. For instance, when scalp EEG recordings are likened to intracranial EEG recordings [53], differences are mainly due to the distinct electrode separation from cerebral source generators [14] and different conductivities of individual skull layers at several scalp locations [15]. Even at the same scale of brain integration the same neuronal assembly exhibits a large variability in the evoked responses to repeated presentation of the same stimulus as a result of changes in the ongoing EEG activity [16]. Despite this large variability among species, individuals of the
same specie, and within the same individual, evidence prompts that synchronization of local and distant networks subserves different functions that are largely preserved throughout the mammalian evolution [17, 18]. Neural patterns of EEG synchrony within the same cerebral structure and across distant brain regions are fundamentally modulated by states of wake and sleep, although important variations exist when electrophysiological features of some state-dependent rhythmic patterns are compared within the order Mammalia.

In this review, neurophysiological correlates of consciousness and cognition are discussed, paying special attention to aspects related to neuronal synchronization at different levels of cerebral integration. Results supporting state-dependent changes in brain dynamics will be highlighted as neurobiological substrates of formal properties of consciousness during sleep.

2. How the brain creates the neural code at different scales of integration

Brain functioning requires the coordinated interplay of billions of neurons via their synapto-dendritic couplings [19]. These patterns of neuronal synchrony are organized into coherent functional groups and differentiated by the coordinated activity of the participant neurons [7]. The term synchrony encompasses a spectrum of neural behaviors with distinct spatial and temporal scales [20]. At the single-neuron level, temporally correlated activity between two neurons indicates a synchronic relationship, with important implications for the system whose modifications have proved to reveal changes in its functional connectivity [21]. This pattern of neural correlation has been suggested to be controlled independently of firing rate and involved in the regulation of the flow of information rather than in its meaning [3]. In support of this hypothesis, MacLeod and colleagues [22] found that oscillatory synchronized neuronal activity in the early olfactory system appears to be critical for fine odour discrimination. Recent studies have also provided evidence that changes in neural synchrony can be predictive in nature. Thus, simultaneous recordings of multiple neurons in the primary motor cortex of monkeys during performance of a delayed reaching task showed that motor and premotor neurons fired in synchrony during preparatory delay periods. Neural synchronization augmented as the expectancy period was longer, and was more precise when the stimulus cue approached. Neither changes in neuronal synchrony were accompanied by similar modulation of firing rates, but often went along with oscillatory patterning in local field potentials [23]. Together, these findings suggest that generation of temporal synchrony patterns at the neuronal level might be critically involved in dynamically organizing the neuronal assemblies during specific cognitive and motor processes.
Local integration processes occur in neuronal assemblies distributed over a spatial scale inferior to 1 cm [7]. Neurons monosynaptically connected within several millimeters between areas situated at the same level of the network have shown synchronization in columns of the primary visual cortex and in Brodmann areas 17 and 18 of the cat during wakefulness and REM sleep [24]. Based on the hypothesis that local mechanisms of neural synchrony are functionally necessary for integrating stimulus physical features in a unitary percept [25], different studies found that neurons distributed across distinct columns within the same or different visual regions synchronized selectively their responses during context-dependent selection and perceptual grouping processes [26, 18]. Spontaneous rhythmic oscillations can also be locally generated by intrinsic mechanisms in neocortex or arise as an emergent property of a neuronal network that, as individuals, are non-rhythmic. These local networks of neocortical neurons are thought to be exclusive pacemakers for some EEG rhythms, like alpha (8-13 Hz) and fast oscillations in the gamma range (35-100 Hz) [27].

Intracranial (iEEG) recordings also provide a direct measurement of synaptic communication keeping a high spatial resolution effectively limited by electrode size and spacing [28]. Typically, iEEG recordings can either be made with surface strips or grids of electrodes, or with stereotactically placed depth electrodes [29]. Both electrode diameter and spacing between iEEG electrodes range from approximately several mm to 1 cm which allows the determination of the neuronal dynamics at multiple spatial and temporal scales in the human nervous system [14]. iEEG recordings blur the individual contribution of participating neurons but highlight their common action because of their synchronized responses and topographic arrangement of neurons [28]. Continuous fluctuations in neural co-operation capacity are present not only in response to external stimulation but also in absence of stimulation as occurs during sleep states. Therefore, changes in neuronal coupling at different spatial scales have been related to specific aspects of sensory, motor, and cognitive processing during active wakefulness [7], although they might also explain cognitive differences between wake and sleep states.

Inherent in the concept of the large-scale cortical integration is the premise that neurons in different areas become functionally connected while carrying out the complex operation of the network. The functional connection between these areas implies that they are coactive, and further, that their activity is interdependent. It requires that they be anatomically connected, but many pathways might be responsible for the anatomic connections, including monosynaptic and polysynaptic pathways between the two areas, either unidirectional or reciprocal, as well as divergent feedforward pathways from other regions. Since cortical areas are almost exclusively connected by
excitatory synapses between pyramidal cells and most connected areas are reciprocally coupled, bidirectional excitatory interactions between areas presumably are an important feature of cortical network dynamics. Recursive interactions between cortical areas may allow multiple local networks to temporarily combine into larger processing units in order to accomplish information transactions that require contributions from all of them [30].

Evidence of large-scale cortical integration has been shown by using scalp-EEG and magnetoencephalographic (MEG) recordings in humans. Because scalp-EEG/MEG signals reflect the joint activation of large neurons clusters they are ideally suited to the detection of synchronization between widely spaced neuronal populations [31]. In this context, Rodriguez and collaborators [32] found that face perception induced a long-distance pattern of synchronization between parieto-occipital and fronto-temporal cortical regions within the gamma range (30-40 Hz) corresponding to the moment of perception itself. This long-range pattern of synchronization was absent during the no-perception condition. Patterns of long-range theta (4-7 Hz) synchronization between prefrontal and posterior association cortex has also been associated with retention periods during a working memory task [33], bridging with single-cell studies where prefrontal and parietal neurons showed matching patterns during the delay period in working memory tasks [34, 35].

On the other hand, parallel synchronization within multiple frequency bands has been suggested in order that different dimensions of the cortical integration process coexist simultaneously. Supporting this hypothesis, von Stein and Sarnthein [36] found an increased inter-areal coherence between theta (4-7 Hz) and alpha (8-12 Hz) bands during mental imagery. Their results point out the involvement of low EEG frequencies in the complex interactions underlying top-down processing in humans. Additionally, a prominent phase coupling between gamma frequencies in area 17 and theta and alpha ranges in area 7 of the cat visual cortex has been reported during exposure to stimuli with behavioral relevance [18]. These studies raise the possibility that multi-frequency couplings between spaced brain regions play a key role in the formation of dynamic links as part of large-scale integration cerebral processes.

3. State-dependent modulation of local and large-scale EEG phenomena in humans

Growing evidence suggests that different patterns of brain oscillations underlie processing of specific sensory and cognitive features [37, 38, 39, 40, 41, 42], as well as the generation of different brain states [43, 44, 45], both in animals and humans. Spatiotemporal dynamics of scalp and iEEG phenomena vary from one brain state to another [46, 47, 48], and depending on the specie
under study [49, 50]. Given the functional relevance of hippocampal theta oscillations in sensorimotor integration, memory, and learning processes, mostly revealed by rodent studies, it seems important to determine if oscillations in the human theta range (4-7.5 Hz) can be recorded in the hippocampus and if their behavioral correlates in humans are the same as in other mammals. On the other hand, the synchronous occurrence of gamma oscillations (30-100 Hz) at different spatial scales, mainly observed during sensory and higher cognitive processing performed during active wakefulness, strongly support the existence of distributed oscillatory systems participating in different processes of the same cognitive operation. State-dependent modulations of gamma coupling at different spatiotemporal scales within the human brain might provide useful insights into the neurobiological correlates of cognition in different consciousness states.

The case of state-dependent theta oscillations

Neural oscillations within the 4-12 Hz range have been defined as the “on-line” state of mammal hippocampus [51]. This rhythmic neural behavior, so-called rhythmic slow activity or hippocampal theta oscillations, has been described in non-primate species, including rodents, rabbits, cats and dogs [49, 50], as well as in non-human [52] and human primates [47], although electrophysiological features and behavioral correlates of theta waves show important differences among species. Diverse arguments have been proposed to account for these specie differences regarding the generation sources of hippocampal theta oscillations. Some authors have suggested that the ability to detect hippocampal theta oscillations critically depends on the location of electrodes within this structure, independently of the specie. Others have attributed the difficulty of recording theta oscillations in the primate hippocampus to the loss of the dorsal hippocampus in these species, or even to a “close-field” structure for the theta generation within the hippocampus which would impede detecting the theta oscillations if the electrode is outside of the field boundaries [49].

Extracellular potentials recorded with intracranial electrodes located in neocortical regions and hippocampus of epileptic patients have been demonstrated as being useful in studying oscillatory patterns occurring in spatiotemporal coherent neuronal populations within these cerebral structures [48, 53, 54, 55, 56, 57]. However, evidence regarding the existence of theta oscillations in the human hippocampal formation are elusive and highly controversial [58, 59, 60, 61]. Two different experimental approaches have been employed to determine the presence of theta oscillations in the human brain. On the one hand, and given the role of hippocampal theta oscillations in spatial cognition and voluntary motor behaviors in rodents, human intracranial and magnetoencephalographic experiments have been designed to determine if
these oscillations are affected by different aspects of spatial tasks [62, 63, 64]. On the other, and based on the spontaneous generation of hippocampal theta oscillations during waking and REM sleep in lower mammals, iEEG studies have directly assessed the existence of state-dependent theta oscillations in the human neocortex and hippocampus [47].

Neuroimaging findings have pointed out the critical role of human hippocampus in spatial cognition [65, 66], which is consistent with the traditional view of this brain region as a cognitive map providing the basis for spatial memory and flexible navigation [67]. Unfortunately, only few human studies have reported neurophysiological correlates of spatial navigation [62, 63, 64], but none of them have provided direct evidence supporting involvement of human hippocampal theta oscillations in spatial cognition. For instance, Kahana and collaborators [64] recorded EEG from subdural electrodes while the patients navigated through a virtual reality maze. They found episodes of human theta oscillations (4-8 Hz) in multiple neocortical regions (including the surface of the temporal lobe, but not hippocampus) that were more frequent in more complex mazes and during retrieval of spatial information. Similar association between human theta oscillatory activity and the performance of navigational tasks was confirmed by using MEG recordings [63]. These authors found enhanced theta power (maximum power peak in 3.7 Hz) selectively linked to navigation protocols as compared with control tasks (motor task, passive viewing of the same maze used in the spatial task, and mental concentration task). The magnetic field topography of spatial-theta oscillations was often highly dipolar, implicating temporal and parietal generation sources [63]. All together, these results support the role of human theta oscillations in the processing of spatial information, and in particular in maintaining a representation of the environment suitable for guiding navigation. Whether these oscillations are generated within the human hippocampus is still controversial and should be confirmed with further intracranial studies using depth probes located in different structures of this cerebral structure.

Hippocampal theta oscillations have been traditionally related to voluntary movements in rodents, although this association has not been extensively replicated in humans. Using intracranial depth recordings from one epileptic patient, Arnolds and colleagues [68] found a significant increase in the theta band (maximum peak around 3-4 Hz) of the hippocampal EEG associated with walking in a similar way to that of lower mammals. Intriguing results were reported in other human single-case studies where hippocampal EEG showed a desynchronized pattern simultaneously with voluntary motor behavior. This electrophysiological correlate was, however, suggested as an abnormal activity pattern caused by the epileptic disorder [69]. Although much more evidence is necessary to assume that hippocampal theta in humans is modulated by motor
behavior, it seems obvious that hippocampal theta oscillations accompanying gross voluntary types of movements in rats are not homologous in humans.

In lower mammals, hippocampal theta oscillations have demonstrated to be a reliable correlate of certain behavioral states, emerging as a fundamental electrophysiological feature of wakefulness and REM sleep [50]. Previous research using invasive EEG recordings from epileptic patients have failed to provide evidence of 4-7 Hz theta activity in the human brain during sleep, although rhythmic activity out of the theta range has been found in several studies [58, 59, 60, 61]. For instance, Bodizs and collaborators [58] reported a significant increase in relative power within the 1.5-3 Hz band in parahippocampal gyrus during REM as compared with slow wave sleep (SWS) and wakefulness. Other authors have found faster activities (10-20 Hz) in the medial temporal lobe during both wakefulness and REM sleep, but not in SWS [61]. Although the behavioral aspects of these findings are similar to the sleep-wake correlates of theta rhythm in animals, the difference in frequency range makes it premature to consider human oscillatory activities within the delta [58] and/or alpha-beta [61] bands equivalent to the animal hippocampal theta rhythm, or even to the state-dependent theta (4-7 Hz) found in human scalp EEG studies during waking and REM sleep.

Recent findings obtained with subdural and depth recordings from epileptic patients have shown the first evidence of state-dependent hippocampal theta waves (4-7 Hz) in humans [47]. Unlike the continuous theta in rodents, these oscillations were consistently observed during REM sleep in short (~1 s) bursts (Fig. 1a), and during transitions to wake in longer epochs (Fig. 1b). Theta waves were also observed in the basal temporal lobe and frontal cortex during transitions from sleep to wakefulness and in quiet wakefulness but not in REM sleep (Fig. 1c), and they were not coherent with hippocampal theta oscillations. The absence of functional coupling between neocortex and hippocampus during theta periods indicates that multiple theta generators exist in the human brain, and that they are dynamically regulated by the brain state [47].

These findings demonstrate that theta oscillations are also a prototypical feature of human REM sleep, although they appear transiently as compared with other lower mammals, and their appearance is restricted to the hippocampal formation. The phasic nature of hippocampal theta activity seen during human REM sleep is different from the tonic activity seen in rodents, but similar to the short bouts of theta activity recorded from the basal dendritic side of CA1 in monkeys under urethane anesthesia [52], pointing again to clear differences between lower and higher mammals with respect to the brain mechanisms involved in the generation of theta oscillatory activity.
Figure 1. State-dependent theta oscillations generated in the hippocampus and different neocortical regions. Example of unfiltered EEG trace containing hippocampal theta oscillations associated with REM bursts (A) and awakenings (B) in one patient with depth electrodes placed within the hippocampal formation. Human theta oscillations in frontal, prefrontal and different structures of basal temporal lobe during quiet wakefulness (C). Right panel: Heavy lines represent averaged spectra for all theta epochs in a specific derivation, and light lines correspond to spectra for single epochs shown in A, B, and C, separately. Peak frequencies are for averaged spectra. Figure modified with permission from [47].

The case of state-dependent gamma oscillations

Gamma oscillations in cortical structures have received special attention because of their role in sensory binding, attentional selection, and conscious experience [31, 38, 44]. The same pattern of oscillations are also prevalent in the hippocampal formation, where they have been proposed as assisting in encoding and retrieving memory traces [70].
Oscillations in the gamma frequency band typically appear in brain states characterized by active cognitive processing, regardless of external percepts or internal thoughts and images. For instance, human magnetoencephalographic studies have shown continuous gamma waves spreading over the entire cortical mantle during both wakefulness and REM sleep [44]. The function of gamma oscillations remains uncertain. Whereas short-range gamma synchronization seems to underlie perceptual binding [31], long-range coupling of cortical areas seems to subserve the integration of cognitive processes [7, 32, 71].

Cognitive processes contributing many aspects of consciousness are profoundly altered during sleep. Indeed, perception and attention are remarkably impaired in sleep states. In addition, the prevalence of thoughts decreases from waking through sleep onset and NREM sleep, reaching its nadir in REM sleep, while hallucinations and emotions are enhanced [72]. Recent evidence from human iEEG recordings showed drastic state-dependent changes in gamma (35-58 Hz) functional coupling between brain regions separated by several centimetres (long-range dynamics) and between neuronal populations separated by 1 centimetre within the same cerebral structure (local neural dynamics) [48]. More specifically, gamma EEG coherence in the neocortex was significantly higher during wakefulness as compared with sleep states (slow wave sleep and REM sleep) for both local- and long-range cortical connections (Fig. 2a,b). On the other hand, the hippocampus maintained relatively high levels of local gamma coherence in both SWS and REM sleep, although gamma coherence within hippocampal electrodes was always higher in wakefulness than in either sleep state (Fig. 2d). In contrast, gamma coherence between the hippocampus and different neocortical regions fell dramatically from wakefulness to both SWS and REM sleep (Fig. 2c) [48].

The total absence of cross-talk within and between different cortical regions in the gamma range, seen in both REM and SWS, correlates well with brain states characterized by continuous cognitive disruptions, with important deficits in attention, memory and perceptive functions, and an inability to create a global awareness of the world or the self. These results support previous human scalp EEG evidence of uncoupled fast activity (27-48 Hz) between frontal lobe and perceptual cortical regions during human REM sleep. Gamma EEG coupling between frontal and perceptual regions was enhanced during wakefulness as compared with sleep states [73].

Rhinal-hippocampal gamma coherence has also been reported to be reduced during human sleep as compared with wakefulness, which accounts for the deficiency of declarative memory typically observed during sleep [74]. State-dependent changes in synchronous gamma interactions between hippocampus and neocortex may reflect the action of a gating mechanism which provides a cognitive context based either more in the sensory world (wakefulness), or restricted to internal cognitions (sleep). Thus, changes in
Figure 2. State-dependent gamma EEG coherence across patients at different spatial scales. Gamma (35-58 Hz) coherence was obtained using all possible combinations of cortical electrodes located within 1 cm (A), and between cortical electrodes with a separation above 1 cm (B). Neocortico-hippocampal gamma synchrony was obtained between each hippocampal electrode and each electrode located in neocortex (C). Gamma synchrony within hippocampus was obtained by using all possible combinations of electrodes placed in the hippocampal formation for each patient. Normal curves are superimposed on the frequency histograms. Coherence values range from 0 (absence of functional relationships) to 1 (totally coupled). Figure modified with permission from [48].
thalamo-cortical binding in the gamma range might be functionally involved in mediating arousal and sensory regulation whereas cortico-hippocampal gamma coupling might facilitate the presence of specific cognitive features associated with each brain state. These results provide support for the hypothesis that changes in local- and long-range gamma synchrony are the neurophysiological substrate of cognitive dysfunctions during sleep.

4. Conclusions

Significant progress has been made during the last few years in studying the dynamics of the brain at the microscopic level (single-neuron, single-synapse, single-molecule), but there has been less progress in understanding macroscopic brain dynamics, revealed by the scalp electroencephalogram (EEG), local-field potentials from intracranial recordings (iEEG), and event-related potentials (ERPs). Coherent dynamic phenomena of cerebral activity have been shown at scales ranging from local networks (thousands of neurons) to entire brain regions (millions of neurons) providing insights into the neural mechanisms underlying functional segregation and integration at different spatial scales. The present review examines how state-dependent theta and gamma oscillations might contribute to reveal neural mechanisms of consciousness and cognition in sleep. These results together with others coming from human neuroimaging studies highlight the possibility of approaching the study of formal features of consciousness and cognitive function during sleep states.

Bibliography


