Slow EEG rhythms and inter-hemispheric synchronization across sleep and wakefulness in the human hippocampus

Fabio Moroni, Lino Nobili, Fabrizio De Carli, Marcello Massimini, Stefano Francione, Cristina Marzano, Paola Proserpio, Carlo Cipolli, Luigi De Gennaro, Michele Ferrara.

Abstract

Converging data that attribute a central role to sleep in memory consolidation have increased the interest to understand the characteristics of the hippocampal sleep and their relations with the processing of new information. Neural synchronization between different brain regions is thought to be implicated in long-term memory consolidation by facilitating neural communication and by promoting neural plasticity. However, the majority of studies have focused their interest on intra-hippocampal, rhinal–hippocampal or cortico-hippocampal synchronization, while inter-hemispheric synchronization has been so far neglected.

To clarify the features of spontaneous human hippocampal activity and to investigate inter-hemispheric hippocampal synchronization across vigilance states, pre-sleep wakefulness and nighttime sleep were recorded from right and left homologous hippocampal loci using stereo-EEG techniques. Hence, quantitative and inter-hemispheric coherence analyses of hippocampal activity across sleep and waking states were carried out. The results showed the presence of delta activity in human hippocampal spontaneous EEG also during wakefulness. The activity in the delta range exhibited a peculiar bimodal distribution, namely a low frequency non-oscillatory activity (up to 2 Hz) synchronized between hemispheres mainly during wake and REM sleep, and a faster oscillatory rhythm (2–4 Hz). The latter was less synchronized between the hippocampi and seemed reminiscent of animal RSA (rhythmic slow activity). Notably, the low-delta activity showed high inter-hemispheric hippocampal coherence during REM sleep and, to a lesser extent, during wakefulness, paralleled by a (unexpected) decrease of coherence during NREM sleep. Therefore, low-delta hippocampal state-dependent synchronization starkly contrasts with neocortical behavior in the same frequency range. Further studies might shed light on the role of these low frequency rhythms in the encoding processes during wakefulness and in the consolidation processes during subsequent sleep.

Introduction

The hippocampal formation has been extensively investigated on behalf of its central role in the declarative memory formation (Carr et al., 2011; Eichenbaum, 2004). Our knowledge about the electrophysiological features of hippocampal activity is largely derived from animal studies. To date, hippocampal network activity has been divided into two mutually exclusive activity patterns: the rhythmic slow activity (RSA or theta; 4–10 Hz) associated with gamma oscillation (~200 Hz), denominated ripples (Bland, 1986; Buzsáki, 1986, 2002; Buzsáki et al., 1986; Vanderwolf, 1969). These patterns show distinct behavioral correlates: RSA emerges during exploratory behavior and REM sleep, while LIA is prevalent during consummatory behavior, immobility and slow wave sleep (SWS).

In humans, the number of studies in which the hippocampal electrophysiological activity has been directly investigated is scarce and prevalently limited to patients with pharmaco-resistant epilepsy. These data point to some similarities between the human and the well-known animal hippocampal activity, yet with some relevant differences.

Human cortical theta oscillations, typically defined to be in the 4-8 Hz range (Niedermeyer and Lopes da Silva, 1999), have been observed during a variety of learning tasks, including the encoding (Fell et al., 2003), recognition (Raghavachari et al., 2001) and recall of verbal stimuli (Sederberg et al., 2003). Theta activity has also been...
shown to increase during virtual spatial navigation tasks (Caplan et al., 2001; Ekstrom et al., 2005; Kahana et al., 1999; W atmos et al., 2011).

Nevertheless, some differences between human hippocampal theta rhythm and animal RSA have been reported as far as its duration and generators are concerned (e.g., Cantero et al., 2003; Clemens et al., 2009). Moreover, the comparison between animal and human hippocampal activity during sleep led to the description of a slower (0.5–3 Hz) rhythmic oscillation in the hippocampal region that was present not only during SWS, but also during REM sleep (Bódizs et al., 2001; Clemens et al., 2009; Moroni et al., 2007). These findings suggested that, in humans, hippocampal delta, rather than theta, might be the counterpart of animal RSA, with a slower frequency possibly due to a larger brain size (Buzsáki, 2006; Clemens et al., 2009; Moroni et al., 2007).

In keeping with this view, previous studies on human theta activity have often reported a comparable behavioral modulation of the delta band (1–4 Hz). For instance, Babiloni et al. (2009) reported that hippocampal peak EEG frequency during encoding of a verbal memory task fell within the delta range in 4 of the 5 subjects they examined. Similarly, during a virtual navigation task significant hippocampal movement-related oscillations in the delta range have been observed (Ekstrom et al., 2005; W atmos et al., 2011). A number of other human intracranial studies of the hippocampus have also reported, often overlooked, low-frequency effects based on peak power, coherence, and neuronal phase-locking measures (Arnolds et al., 1980; B riazor, 1968; Jacobs et al., 2007; Mormann et al., 2008; Rutishauser et al., 2010).

Oscillatory dynamics within and between cerebral regions are implicated in waking cognitive processes such as memory and perception (e.g., Fell et al., 2001). In particular the phase synchronization, i.e. the synchronization of oscillatory phases between different brain regions, supports long-term memory and acts by facilitating neural communication and by promoting neural plasticity (Fell and Axmacher, 2011).

In waking, it has been shown that the synchronization of neural assemblies in different frequency ranges induces specific forms of cellular plasticity during subsequent stages of memory formation (Axmacher et al., 2006). It can be hypothesized that similar mechanisms may work also during sleep, as suggested by several findings from animal studies. Indeed, using simultaneous recordings from an array of hippocampal cells in rodents, it has been shown that both the spatial and temporal sequence of firing activity between cell pairs recorded during behavior is significantly preserved during subsequent sleep (Lee and Wilson, 2002; Louie and Wilson, 2001; Skaggs and McNaughton, 1996; Wilson and McNaughton, 1994).

In humans, large-scale EEG synchronization has been always studied intrahemispherically, between medio-temporal lobe (MTL) structures (e.g., hippocampal–parahippocampal: Fell et al., 2001, 2003; Le van Quyen et al., 2010) or between the neocortex and the hippocampal region (Clemens et al., 2007, 2011; Wagner et al., 2010). Interestingly, some findings suggest that rhinal–hippocampal connectivity may be crucial in determining declarative memory formation also during sleep. A successful memorization of dreams is indeed accompanied by an enhanced rhinal–hippocampal and intrahippocampal EEG coherence, pointing out a common neurophysiological mechanism between wakefulness and sleep (Fell et al., 2006). Consistently, the reduction of rhinal–hippocampal coherence during sleep compared to wakefulness has been suggested as a possible electrophysiological substrate of the sleep-related deficit of declarative memory (Fell et al., 2003).

Also surface EEG recordings have provided sparse evidence on the relationship between memory processes and different EEG parameters. For instance, an increase of mean spectral amplitude and of EEG coherence in the delta range has been reported in scalp recordings during both auditory and visual memory tasks as a function of successful recalling (Weiss and Rappelsberger, 2000).

Interestingly, a better performance in terms of number of recalled nouns was correlated with an increase of long-range (inter-hemispheric) synchronization (Weiss and Rappelsberger, 2000).

However, to our best knowledge, inter-hemispheric coherence between hippocampi has been never investigated so far in animals as well as in humans. Here, we assessed the inter-hemispheric hippocampal coherence in a group of 4 rare epileptic patients undergoing stereo-EEG (SEEG) recordings, during presurgical electro-clinical evaluation, from two homologous bilateral hippocampal derivations.

As a preliminary analysis, we extended our previous (uni-hemispheric) results (Moroni et al., 2007) by evaluating the presence of inter-hemispherical differences in hippocampal SEEG power values. In addition, we compared right and left hippocampi not only during NREM and REM sleep, but also during wakefulness. Then, we specifically assessed whether the different vigilance states (wakefulness, NREM and REM sleep) are characterized by changes of EEG synchronization between the hippocampi, in particular in the low frequency range, based on the hypothesis that higher EEG coherence could tend an inter-hemispheric transfer of information, irrespective of the vigilance state.

Materials and methods

Subjects

Four male patients (mean age: 27±7.8 years, age range: 20–38 years, see Table 1) with pharmacoresistant focal epilepsy underwent an individualized investigation with stereotactically implanted intracerebral multilead electrodes for an accurate definition of the epileptogenic zone for surgical purposes (see Cosso et al., 2005 for details on SEEG methodology). Table 1 summarizes patients’ demographic and clinical data. The sample is peculiar because it includes only participants who did not show features of hippocampal sclerosis and whose SEEG revealed that seizures originated outside the temporal mesial structures.

Sleep was recorded four days after electrode implantation, so that subjects were adapted to the stereotactic implantation and to the procedures for stereo-EEG recordings. During the study patients maintained the standard doses of anticonvulsant medications (for details see Table 1). Before intracerebral electrode implantation, patients gave their written informed consent for participation in this study and for publication of data. The protocol, being part of presurgical clinical evaluation, was approved by the Ethics Committee of the Niguarda Ca Granda Hospital of Milan (Italy).

Electrodes placement and EEG/SEEG recordings

Stereo-EEG activity was recorded from platinum–iridium intracerebral electrodes, with a diameter of 0.8 mm, a contact length of 2 mm and an intercontact distance of 1.5 mm. All the four subjects had two electrode contacts localized unequivocally within the right and left homologous hippocampi. The placement of electrode contacts was ascertained by post-implantation magnetic resonance imaging (MRI) scans (for location details see Table 1). Scalp EEG activity was recorded from two platinum needle electrodes placed during surgery at “10–20” positions Fz and Cz on the scalp. Electrooculogram (EOG) activity was registered at the outer canthi of both eyes and submental electromyographic (EMG) activity was acquired with electrodes attached to the chin.

EEG and SEEG signals were recorded using a 24 channels ambulatory system recording (XLTEK, Trex®) with a sampling rate of 200 Hz.

Procedure

The study began at 8 p.m. Patients were connected to the polygraph and the recording started. Then patients were free to decide...
when going to sleep. The following morning at 7.30 a.m. patients were disconnected and EEG–SEEG data were downloaded from the portable device memory card and stored on the hard disk of a computer.

Data analysis

Acquisition files were converted to EDF (European Data Format) to be handled with a MatLab software (MatLab 7.0, The Matworks, Inc.). This software allowed us to modify montage settings and to apply digital filters to the signal. We used a bipolar montage between contiguous intracerebral electrode contacts and between Fz–Cz scalp electrodes, EOG and EMG derivations. EEG and SEEG signals were filtered and EMG signal was 0.1–15 Hz band pass filtered, EOG signal was 0.1–70 Hz band pass filtered and EMG signal was 5–100 Hz band pass filtered. These filter settings are slightly different from the standard ones (Rechtschaffen and Kales, 1968), but this difference does not give way to sensible visual differences in the raw tracings, which were scored according to the standard criteria (Rechtschaffen and Kales, 1968). The same custom software allowed us to score sleep stages, to manually remove artifacts and to run power and coherence analysis.

Sleep and preceding wake were scored in 20 s epochs. Periods with interictal spikes and pathological EEG signals were marked in order to remove them from the subsequent analyses.

Preliminary SEEG power spectra analysis

Spectral power for each hippocampal derivation signals was computed using the Fast Fourier Transform (FFT — Welch method) applied to 4-s segments (Tukey window), with an overlapping period of 2 s, in the frequency range of 0.5–30.0 Hz. Then, resulting power spectral density was averaged in 20-s epochs. NREM sleep included stages 2, 3 and 4.

To assess inter-hemispherical differences within each state (wakefulness, NREM and REM sleep), we compared right and left hippocampal EEG power values for each frequency bin by means of two-tailed Student’s t tests, separately for each state. To correct for multiple comparisons, a Bonferroni correction was applied and the alpha level was then adjusted to p ≤ 0.009.

Moreover, power density values in the low frequency range (grouped in two frequency bands) were submitted to a repeated measure ANOVA with Hemisphere (left and right hippocampus), State (wakefulness, NREM and REM sleep) and Frequency band (low-delta: 0.5–2.0 Hz; high-delta: 2.0–4.0 Hz) as factors.

Hippocampal inter-hemispheric coherence and time course across the wake–sleep cycle

To investigate inter-hemispheric functional connectivity, spectral coherence between two homologous hippocampal derivations was computed using the Welch-averaged modified periodogram method in the frequency range of 0.5–30.0 Hz. The Fast Fourier Transform was applied to 4-s segments (Tukey window) to compute the power spectral density of the two signals and their cross-spectral density; then, each of them was averaged in 20-s epochs.

Since the low delta range (0.5–2.0 Hz) exhibits higher coherence values compared to faster frequencies (see Results), a subsequent analysis on the time course of SEEG power and coherence across wake/sleep periods was limited to this frequency range. To this aim, the first three NREM–REM cycles (this was the minimum common number of cycles, see also Moroni et al., 2007), and the pre-sleep wakefulness were divided into an equal number of intervals (10 steps for each pre-sleep wakefulness; 10 steps for each NREM period and 3 steps for each REM period).

To further investigate inter-hemispherical phase relationships in the low-delta range, we performed an analysis of phase coupling of slow waves detected in the hippocampal derivations, by applying an algorithm for the automatic low-delta waves negative peak detection (Molle et al., 2002; Massimini et al., 2004; see Supplementary Materials for methodological details).

Oscillatory aspects of human hippocampal activity

Finally, to ascertain whether hippocampal SEEG activity is characterized by rhythmic oscillatory patterns (similar to rodents’ RSA), or by transient phenomena (e.g. LIA activity), we applied the Better OSCillation (BOSC) detection method (Caplan et al., 2001; Whitten et al., 2011) to three selected samples of SEEG signals (~20 min each). The first sample was selected from the pre-sleep resting wakefulness period, 1 h before sleep onset. The second sample was selected from the central part of the first NREM period, characterized by the highest amount of SWS. In particular the selected periods had a mean of 28% in stage 4, 49% in stage 3 and 23% in stage 2. The third sample coincided with the entire duration of the second REM period.

The BOSC method is aimed to detect oscillatory activity within a signal containing a non-rhythmic portion. BOSC is a robust detection method, which has been successfully used to identify and quantify theta oscillations in the human neocortex (Caplan and Glaholt, 2007; Caplan et al., 2001, 2003) and hippocampus (Ekstrom et al., 2005), which were correlated with memory encoding and retrieval. This method detects oscillatory activity in EEG signals by taking into account the functional form of “background,” non-rhythmic portion of the signal and revealing segments of the recording that deviate significantly from the spectral characteristics of the background.

The analysis was performed separately at each frequency of interest (in the 1–30 Hz range) for right and left hippocampal derivations. Further methodological details are provided in the Supplementary Materials.

Table 1
Demographic, MRI findings and clinical information for each patient.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Medications (mg/day)</th>
<th>MRI</th>
<th>SEEG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sample lobes</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>20</td>
<td>Oxacarbamazepine (1200 mg) Lamotrigin (400 mg) Topiramate (300 mg)</td>
<td>Uninformative</td>
<td>FTI</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>38</td>
<td>Oxacarbamazepine (1500 mg) Levetiracetam (2000 mg)</td>
<td>Uninformative</td>
<td>TPO</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>23</td>
<td>Valproic acid (1500 mg) Phenytoin (200 mg)</td>
<td>Uninformative</td>
<td>FTC</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>27</td>
<td>Carbamazepine (800 mg)</td>
<td>Uninformative</td>
<td>FTI</td>
</tr>
</tbody>
</table>

C = central; F = frontal; O = occipital; P = parietal; T = temporal; I = insular.

* Position of the SEEG derivations submitted to sleep EEG analysis.

* Site of origin of the seizures.
Results

Spectral power across wakefulness and sleep in the two hippocampi

Power spectra analysis of right and left hippocampi showed that high levels of delta power characterize hippocampal signal during NREM and REM sleep. Moreover, a high delta power was present also during wakefulness (Supplementary Fig. 1). The comparison between right and left hippocampi in SEEG power across the 0.5–30.0 Hz range did not show any significant difference between hemispheres (Supplementary Fig. 1).

The presence of a prominent delta rhythm in the hippocampus, during both NREM and REM sleep and even during wakefulness, was clearly evident also at visual inspection of the raw data (Supplementary Fig. 2).

The three vigilance states differed from each other in the low-delta range (0.5–2.0 Hz), with NREM sleep showing the maximum power, followed by REM sleep and wakefulness (for the ANOVA details, see Supplementary Table 1). On the other hand, power in the high-delta range (2.0–4.0 Hz) was significantly higher during NREM sleep than during both wakefulness and REM sleep, which did not differ between them.

NREM delta waves were also of higher amplitude compared to those recorded during wakefulness and REM sleep (Supplementary Fig. 3), as indicated by an automatic detection analysis of delta waves (see Supplementary Methods for more methodological details).

Hippocampal inter-hemispheric coherence and time course of low-delta power and coherence across the wake-sleep cycle

Analysis of coherence showed that the hippocampi are mainly coherent in the low frequency range, while no coherence peak emerges in the higher frequencies. In particular, the first two bins (0.5–1.0 and 1.0–2.0 Hz) showed a high coherence during REM sleep, with slightly lower values during wakefulness and low levels during NREM sleep (Fig. 1). For this reason we performed a further analysis on this narrower frequency range.

The analyses on the time course of the low-delta band (0.5–2.0 Hz) disclosed an opposite pattern between power and coherence values (Fig. 2). During wakefulness, low-delta coherence was moderately high, while low-delta power was comparatively low. At NREM sleep onset, a drop of inter-hemispheric hippocampal coherence paralleled the sharp increase of power. On the contrary, at REM onset, while hippocampal power decreased, inter-hemispheric hippocampal coherence increased. Time series analysis comparing hippocampal power and inter-hemispheric hippocampal coherence showed a significant negative correlation ($r = -0.65, p<0.0001$), revealing a tight relationship between the increase of power in the low-delta range and the decrease of hippocampal low-delta synchronization during all the recording period. The analysis of the phase relationship of low-delta waves confirmed the coherence results, clarifying that no phase delay emerges between right and left hippocampal low-delta activity (Supplementary Fig. 4).

Oscillatory aspects of human hippocampal activity

The last step was to ascertain whether the above reported low-frequency hippocampal SEEG activity is indeed an intrinsically rhythmic oscillation. The BOSC analysis (Fig. 3) revealed that low-delta hippocampal activity (0.5–2.0 Hz) is not an oscillatory rhythm. On the other hand, the BOSC analysis revealed a robust oscillatory activity in the high delta range (2.0–4.0 Hz) across all the vigilance states. A peak in the theta range (4.0–8.0 Hz) is also present during wakefulness. Moreover, a peak in the beta range at 16.0–21.0 Hz is present during wakefulness and REM sleep, while a clear peak in the sigma range (12.0–15.0 Hz) is present during NREM sleep.

Discussion

Here we showed that human hippocampal SEEG activity is characterized by a consistent presence of delta activity also during wakefulness. Since slow EEG rhythms have been traditionally considered as a hallmark of deactivation (sleep), their presence also during the activated states (wakefulness and REM sleep) points to a possible functional differentiation of these rhythms across the wake–sleep cycle.

Another intriguing and novel result is the description of a bimodal distribution of hippocampal delta activity: a faster delta rhythm (2.0–4.0 Hz), strongly oscillatory during all the vigilance states, and a slow delta rhythm (0.5–2.0 Hz), with a peculiar inter-hemispheric behavior. In particular, we showed that the homologous hippocampi are strongly synchronized in the low-delta range during REM sleep, are slightly less coherent during wakefulness, and reach their minimal level during NREM sleep.

Slow EEG rhythms in the human hippocampus across the wake–sleep cycle

Here we confirmed the prominent presence of delta activity during REM sleep in the human hippocampus (Bódizs et al., 2001; Clemens et al., 2009; Moroni et al., 2007), and provided a clear evidence of its existence in the spontaneous EEG also during wakefulness.

Therefore, hippocampal delta activity differs from its cortical counterparts because of the occurrence also during the activated states (wakefulness and REM sleep). Indeed, we found a bimodal distribution of delta activity within the hippocampus. A faster rhythm emerges from the analysis of oscillation detection, that shows the presence of a higher frequency delta rhythm (2.0–4.0 Hz) strongly oscillatory during all the vigilance states. This human hippocampal high-delta, here observed during wakefulness and REM sleep, is reminiscent of RSA in rodents (Bland, 1986; Buzsáki, 1986, 2002). Such a rhythmic delta activity is in tight agreement with recent findings in humans showing a hippocampal oscillatory activity at ~3 Hz during verbal and spatial navigation memory tasks (Babiloni et al., 2009; Ekstrom et al., 2005; Lega et al., 2011; Watrous et al., 2011). It would be interesting to assess whether this hippocampal activity is
related to memory consolidation processes during sleep, or to the encoding of declarative memories within the dream plot, as suggested by a recent surface EEG study (Marzano et al., 2011).

The existence of slow hippocampal rhythms in the activated states in humans is coherent with the results of pioneering chronic studies in rabbits, describing a delta activity in the hippocampus during the arousal state (Green and Arduini, 1954). In humans, Zaveri et al. (2001) compared the background activity at rest of the epileptogenic and the non-epileptogenic hippocampi in patients with different kind of temporal lobe epilepsy (mesial and non-mesial). They observed the presence of a clear-cut peak in delta activity in all (n=14) patients, with a higher amount of delta power density in patients with non-epileptogenic hippocampus. Taken together, these results strongly suggest that the slow SEEG components are not related to the pathologic hippocampal activity and may exist in the normal human hippocampus.

The presence of slow hippocampal oscillations in wakefulness is not necessarily in contrast with its presence during sleep. The functional role of these oscillations may change across states and have a more cognitively meaningful role during wakefulness, for example during the execution of memory tasks (Babiloni et al., 2009; Ekstrom et al., 2005; Watrous et al., 2011). Notably, synchronized discharge of firing in hippocampal neurons, leading to a replay of the neuronal activity observed during spatial learning, has been reported also during resting wakefulness in rodents, and it is intended as a potential contributor to both memory consolidation and retrieval (for a review, see Carr et al., 2011).

We cannot definitively rule out the possibility that the synchronized slow SEEG activity here reported within the human hippocampus may be related to the specific pathology (epilepsy) of our patients and/or to the effects of the medications. Antiepileptic drugs (AEDs) can certainly influence brain electrical activity, although data regarding their effects on hippocampal activity are lacking. In particular, it has been reported that a stable therapy with phenytoin, carbamazepine and phenobarbital could enhance the EEG power of slow rhythms (Besser et al., 1992; Duncan et al., 1989; Meador et al., 1993). Nevertheless, such an increase of slow EEG activity was not always found, at least as carbamazepine and valproic acid are concerned (Arzy et al., 2010). These effects are less evident (or absent) under topiramate (Mecarelli et al., 2001; Neufeld et al., 1999;
Placidi et al., 2004) and absent under lamotrigine and levetiracetam treatment (Marciani et al., 1999; Veauthier et al., 2009). However, in all those studies AEDs did not induce the occurrence of slow frequency peaks that were not already present before the drug treatment. Therefore, it is unlikely that the slow SEEG activity here observed could be a consequence of different AED treatments in a sample of patients characterized by distinct site of origin of the seizures (see Table 1).

Inter-hemispheric hippocampal synchronization: relations to memory?

The presence of a second slow hippocampal rhythm in the 0.5–2.0 Hz frequency band, that shows a peculiar inter-hemispheric behavior, is another novel finding of the study.

Hence, hippocampal delta activity differs from its cortical homologous also because of a different behavior of inter-hemispheric coherence across vigilance states. Coherence analysis indeed showed that right and left hippocampi modify their concordance in the low-delta range across wakefulness, NREM and REM sleep. In particular, homologous hippocampi are strongly phase-related in the low-delta range during REM sleep, are slightly less coherent during wakefulness, and reach their minimal level during NREM sleep.

The drop of inter-hemispheric synchronization of hippocampal low-delta during NREM sleep is an unexpected and intriguing finding. Thus both left and right hippocampi produce slow EEG rhythms during NREM sleep, but they show weak synchronization. It is noteworthy that the time course of hippocampal low-delta power and that of inter-hemispheric coherence in the same frequency range showed an opposite behavior: in fact, the increase of hippocampal power was paralleled by a decrease of the inter-hemispheric hippocampal coherence and vice versa. These data suggest a different physiological meaning of neocortical and hippocampal synchronization in the low-delta range. In fact, this pattern is at odds with the neocortical behavior in the same frequencies inferred from scalp EEG in healthy subjects. In scalp recordings, EEG power and coherence in the low-delta band show a parallel behavior (Achermann and Borbély, 1998), while here they show an inverse behavior in the hippocampi. It may thus be hypothesized that inter-hemispheric low-delta synchronization could be a hallmark of brain deactivation within cortical sites, and of brain activation in the hippocampal formation (Green and Arduini, 1954).

The presence of out-of-phase inter-hippocampal slow EEG rhythms during NREM sleep, which become in phase during REM sleep, could be tentatively interpreted in the framework of the sequential hypothesis of sleep consolidation (Gais et al., 2000; Giuditta et al., 1995). Accordingly, we can differentiate between a system consolidation mainly dependent on SWS and involving wide-spread brain areas, and a local synaptic plasticity referred to REM sleep. SWS system consolidation engages wide cortical and hippocampal circuits that could explain the loss of coherence between hippocampi, here observed. In other words, the neocortical slow oscillation would facilitate a long range transfer of (mainly declarative) information (Diekelmann and Born, 2010). On the other hand, the disentangled, localized nature of synaptic consolidation during REM sleep could explain the rise of inter-hippocampal network synchronization in the low delta range (Diekelmann and Born, 2010).

In any case, the role of human hippocampal slow oscillations, also in relation to analogous cortical rhythms, undoubtedly deserves further attention. In a study combining bilateral single-unit, local field potentials (LFPs) and intracranial electrocorticography recordings in humans, Nir et al. (2008) found slow (~0.1 Hz) spontaneous fluctuations of neuronal activity with significant (cortical) interhemispheric correlations. Notably, the interhemispheric correlations were enhanced during REM and stage 2 sleep.

Although the role of these EEG oscillations in the physiology of sleep is poorly understood, it is believed that they are well suited to coordinate activity across large cortico-cortical networks (Buzsáki, 2006) and that they could, in this way, organize sleep-dependent neuroplastic processes, such as the consolidation of episodic memory. In fact, it has been shown that slow oscillations group a number of other sleep rhythms including hippocampal sharp wave-ripples both in animals and humans (e.g., Clemens et al., 2007; Molle et al., 2006). This interaction between hippocampal and thalamo-cortical networks may provide a temporal framework for information transfer underlying the consolidation of hippocampus-dependent memories during sleep (Buzsáki, 1989, 1998; Gais and Born, 2004; Born et al., 2006).

As the role of the interhemispheric correlated spontaneous fluctuations is concerned (Nir et al., 2008), one intriguing possibility is that they play a role in maintenance and renormalization of synaptic contacts, as suggested for slow-wave activity during sleep (Tononi and Girelli, 2006). In keeping with this view, positive correlations between EEG infraslow oscillations and metabolic activity in the hippocampus and parahippocampal gyri have been recently reported (Picchioni et al., 2011). This pattern, which is observed during all sleep stages, suggests that these oscillations may be important for the sleep-dependent consolidation of memories, endorsing system-level consolidation.

Finally, as a further support to the role of slow oscillations for memory consolidation processes during sleep, we previously reported that intensive learning is followed by an increase in the hippocampal SEEG power in the very low frequency range (0.5–1.0 Hz) (Moroni et al., 2008). The magnitude of performance improvement was significantly correlated with the subsequent SEEG low frequency power increase, suggesting the existence of a direct link between memory consolidation and very low hippocampal rhythms.

Faster EEG rhythms in the human hippocampus

BOSC analysis revealed the presence of other interesting oscillatory patterns, such as a peak in the beta band (16–22 Hz) during wakefulness and REM sleep. The same peak has been recently observed in wakefulness during an episodic memory task (Lega et al., 2011) and a spatial navigation task (Watrous et al., 2011), although the functional role of this beta rhythm remains another unanswered question. It is noteworthy that in three different studies assessing hippocampal oscillatory activity during memory tasks (Lega et al., 2011; Watrous et al., 2011) and pre-sleep wakefulness (present study), a peak at ~3 Hz and another at ~20 Hz have been reported. These strong similarities between independent studies (in an overall sample of 47 patients) point to a quite robust phenomenon and denote the presence of an electrophysiological activity that deserves further investigation. During NREM sleep, we also found a peak in the sigma range that could be ascribed to the presence of sleep spindles in hippocampal sites. A sigma peak is also present in the spectral analysis, prevailing in the right hippocampus (Supplementary Fig. 1). These data are not surprising, as hippocampal spindles were identified in previous studies, even though not in all patients (Clemens et al., 2011; Malow et al., 1999; Montplaisir et al., 1981). The physiological or pathological nature of hippocampal spindles is still not clear. However, the authors who systematically investigated spindle activity in the hippocampus pointed to the conclusion that most examples of hippocampal activity resembling sleep spindles are probably physiologic in origin, originating within the hippocampus or propagating from neighboring regions (Clemens et al., 2011; Malow et al., 1999).

Conclusions

In conclusion, our results suggest that two different types of delta activity are originated in the hippocampus: a low-delta (0.5–2.0 Hz) and a high-delta rhythm (2.0–4.0 Hz). The former appears as a transient rhythm present during all the states, but intriguingly
synchronous between the hippocampi mainly during the activated states (wake and REM sleep). The latter, instead, appears as an oscillatory background hippocampal rhythm present during all the states, but only weakly in phase between hemispheres, at least as far as it emerges from coherence analysis.

Indeed, it is reasonable that a synchronized occurrence of specific oscillations between hippocampi could be driven by different behavioral states. Here, we computed mean coherence over a long period of time, being therefore unable to disentangle between short periods of different behavioral activity. Thus, we cannot exclude variations in the level of synchronization in specific time windows; further studies in which the behavioral correlates of these activities are taken into account are needed. Although our results may indirectly suggest a role of hippocampal slow oscillations for memory consolidation processes during sleep, only specific studies focusing on task-dependent changes of SEEG activity and coherence would be able to provide a more definitive answer.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.11.093.

References


