Procedural learning and sleep hippocampal low frequencies in humans

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A B S T R A C T

Recent evidence suggests that slow EEG rhythms are involved in post-learning plasticity. However, the relationships between memory consolidation and hippocampal EEG features remain unclear. Here, we assessed the effects of both procedural and declarative learning on qualitative and quantitative measures of sleep by recording stereo-EEG (SEEG) directly from the hippocampus and the neocortex in a group of epileptic patients undergoing pre-surgical evaluations. Following a baseline night, sleep was recorded after administration of a declarative (paired-associate word list learning task) and a procedural (sequential finger tapping) task. Patients were tested before going to bed (test) and after sleep in the following morning (retest). At retest, we found that patients recalled correctly more word pairs compared to the pre-sleep test (declarative task), and they were slightly faster in performing the motor task (procedural task). Standard polysonmography showed an increase in the amount of slow-wave sleep (SWS) only after procedural learning, paralleled by an increase of hippocampal SEEG power in the very low frequency range (VLF, 0.5–1 Hz) during the first NREM sleep cycle. Moreover, procedural performance enhancement and SEEG power increase in the hippocampal VLF were significantly correlated, indicating a link between procedural memory consolidation and slow hippocampal SEEG rhythms. These findings are consistent with the hypothesis of synaptic homeostasis occurring during sleep, suggesting that hippocampal slow oscillations are associated with local processes of post-learning synaptic downscaling.

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Introduction

A large body of evidence suggests that sleep is critically involved in the process of memory consolidation (Stickgold and Walker, 2007), but the exact neurophysiological and electrophysiological mechanisms underlying such a complex phenomenon remain unclear. It has been proposed that sleep-related memory consolidation relies on the “replay” of awake experience in both the cortex and the hippocampal complex (Rasch and Born, 2007). According to this theoretical model, it has been shown that, in non-human animals, patterns of neural activity re-emerge spontaneously soon after learning in a state-independent way, i.e. during both quiet waking and sleep (Kudrimoti et al., 1999; Hoffman and McNaughton, 2002). In addition, high-order replay mechanisms, consisting of temporally sequential firing across multiple cells during sleep, have been observed in rodents within the hippocampus during slow-wave sleep (SWS) (Nadasdy et al., 1999; Lee and Wilson, 2002) and rapid-eye-movement sleep (REM) (Louie and Wilson, 2001), as well as in the visual cortex during SWS (Ji and Wilson, 2007). Consistent with these findings, neuroimaging studies in humans have reported re-activation of the hippocampal and mediotemporal structures during SWS following procedural (Maquet et al., 2000) and declarative (Peigneux et al., 2004) learning, which correlated with performance improvement after sleep (Peigneux et al., 2004). These findings provide evidence that sleep, indeed, may play an active and important role in human memory consolidation.

Recently, two studies aimed at investigating the direct relationship between memory consolidation and hippocampal-parahippocampal electrical activity during sleep in humans, providing a direct electrophysiological evidence of memory...
consolidation occurring during sleep. These studies were performed in epileptic patients, who had implanted electrodes in the medial temporal lobe to detect the exact location of epileptic foci. In the first study (Fell et al., 2006), the authors showed that in patients with good dream recall the rhinal–hippocampal EEG coherence values were larger compared to patients with poor dream recall, suggesting that rhinal–hippocampal connectivity is a key factor in determining declarative memory formation. In the second study (Axmacher et al., 2008), the recording of hippocampal event-related potentials indicated that a nap sleep facilitates memory consolidation during post-sleep waking state. Moreover, the authors reported that the amount of delta activity during the nap was positively correlated with individuals' performance in a declarative task. These findings are consistent with the proposed role of slow EEG rhythms in synaptic down-scaling and recovery of synaptic plasticity (Tononi and Cirelli, 2003, 2006; Huber et al., 2004, 2006, 2007), and suggest the need for more detailed electrophysiological investigations assessing the specific relationships between different types of memory consolidation and hippocampal EEG features.

In the present study, we investigated the effects of both procedural and declarative learning on the qualitative and quantitative measures of sleep as recorded from the hippocampus in a group of epileptic patients undergoing pre-surgical evaluations. If the hippocampus is directly involved in the memory consolidation process, we expect significant changes in the hippocampal stereo-EEG (SEEG) slow rhythms, as suggested by the functional link between sleep EEG low frequencies and post-learning plasticity (Aeschbach et al., 2008; Vyazovskiy et al., 2008).

Materials and methods

Subjects

Eight patients (1 female, mean age: 28±8.1 years, age range: 18–40 years) with pharmaco-resistant focal epilepsy participated in this study. For surgical purposes, the patients underwent an individual investigation with stereotactically implanted intracerebral multilead electrodes for a precise localization of the epileptogenic zone (see Cossu et al., 2005 for details on SEEG methodology). In Table 1 we reported the patients’ demographic and clinical information. None of the patients showed signs of hippocampal sclerosis, and SEEG revealed that seizures originated outside the temporal mesial structures. The patients underwent the Raven’s Coloured Progressive Matrices (Raven, 1996) to exclude for possible cognitive impairments (scores above 95th percentile). All patients were right handed (scores >0.70), as assessed by a lateral preference questionnaire (Salmaso and Longoni, 1985). In a preliminary evaluation, we assessed the capability of the patients to perform the memory tasks: patients who were not able to carry out properly a practice version of the experimental tasks were not included in the study. During this study patients continued taking their standard doses of anticonvulsant medications (for details see Table 1). Before intracerebral electrode implantation, patients gave written informed consent as approved by the local Ethical Committee of the Niguarda Ca Granda Hospital.

Electrode 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. Each patient had at least two electrode contacts that could be localized unequivocally within the hippocampus and the neocortex. The individual placement of electrode contacts was ascertained by post-implantation magnetic resonance imaging (MRI) scans (for individual location details see Table 1). Fig. 1 shows exemplar MRI coronal and sagittal views of intracranial electrodes implanted in the hippocampus.

Scalp EEG activity was recorded from two platinum needle electrodes placed during surgery at “10–20” positions Fz and Cz on the scalp. Electroocular activity was registered at the outer canthi of both eyes, and submental electromyographic activity was acquired with electrodes attached to the chin. EEG and SEEG signals were recorded using a 24-channel ambulatory system recording (XLTEK, Trex™) with a sampling rate of 512 Hz.

### Table 1

Patients’ demographic and clinical data, and MRI findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Medications (mg/day)</th>
<th>MRI findings</th>
<th>SEEG</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Side</td>
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<tr>
<td>1</td>
<td>M</td>
<td>40</td>
<td>Carbamazepine (800)</td>
<td>Unrevealing</td>
<td>Left</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>31</td>
<td>Carbamazepine (800)</td>
<td>Bilateral subependymal nodular periventricular heterotopia</td>
<td>Right</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>27</td>
<td>Carbamazepine (1600)</td>
<td>Right O cortical dysplasia</td>
<td>Right</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>18</td>
<td>Carbamazepine (800)</td>
<td>Unrevealing</td>
<td>Left</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>19</td>
<td>Levetiracetam (2000)</td>
<td>Unrevealing</td>
<td>Right</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>28</td>
<td>Carbamazepine (800)</td>
<td>Right TO cortical dysplasia</td>
<td>Right</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>38</td>
<td>Levetiracetam (5000)</td>
<td>Bilateral cortical malformations (tuberosum)</td>
<td>Left</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>23</td>
<td>Oxcarbazepine (1800)</td>
<td>Right O ischemic lesion</td>
<td>Right</td>
</tr>
</tbody>
</table>

C = central; F = frontal; O = occipital; P = parietal; T = temporal.
* Indicates the positions of the SEEG derivations included in the sleep EEG analysis. ** Indicates the sites in which epileptic seizures originated.
Procedure

Sleep SEEG/EEG recordings have been carried out during three non-consecutive nights (one baseline and two experimental). During the first night (three days after electrode implantation), baseline undisturbed sleep was recorded. Recordings began at about 8.30 pm, when the electrodes were connected to a portable polygraph. Then, the patients were left free to decide when to go to sleep. The following morning, at 7.30 am, the electrodes were disconnected from the polygraph and sleep data were downloaded for further analyses. The following night (experimental 1) at about 8.30 pm, electrodes were reconnected to the polygraph and patients were required to perform one memory task, namely the declarative or the procedural task, taking approximately 20–30 min. After the task was completed, the patients were again left free to decide when to go to sleep. The following morning, one hour after awakening, the patients were retested on the same task. This first experimental night was followed by an undisturbed night of sleep (third night) to avoid any possible interference between the two experimental manipulations. Finally, the fourth night (experimental 2) the patients underwent an identical recording procedure as for the second night, except for the memory task performed. The tasks were administered in a counterbalanced order between patients. For the entire duration of this study, the patients were under clinical observation, and they did not perform any neuropsychological or neurological assessment, which might have interfered with the experimental protocol. During daytime they were not allowed to sleep, but they were permitted to read, watch television, play cards or relax.

Declarative memory task

We used a paired-associate word list learning task (PAWT) to assess declarative learning (Plihal and Born, 1997; Gais and Born, 2004). The list consisted of 40 pairs of semantically related Italian nouns, which the subject had to learn to a criterion of at least 60%. Each paired-associate word, consisting of a stimulus and a response word, was matched in length, emotionality, meaningfulness and concreteness. Word pairs were individually and randomly presented on a 19-inch computer screen (3 s for each pair), with an interstimulus interval of 500 ms. Patients were requested to read each word aloud and memorize the pairs. After presentation of the complete list, cued recall was tested. In this phase of the experiment, the 40 stimulus words (one word for each pair) appeared on the screen in a different random sequence. For each stimulus word, the patients were required to name the response word, with unlimited response time. After each response, the correct answer was displayed for 2 s (no matter whether the response was correct or not), and the experimenter recorded the patient’s response. If 60% criterion for correct responses was not achieved, the recall testing was repeated. Subjects were then informed that the following morning they would undergo a further memory test, about 60 min after awakening.

The number of word pairs recalled on criterion trial (pre-sleep) and during retest in the following morning (post-sleep) was treated as dependent variable. The first and last two pairs of the list were not included in the analysis to avoid primacy and recency effects.
Procedural memory task

To evaluate the procedural memory domain, we used a sequential finger tapping task (SFTT) (e.g., Walker et al., 2002). The task is a computerized version of a previous test that has been proven to enable delayed learning 24 h after learning (Karni et al., 1998). The SFTT requires the subjects to press four numeric keys on a standard computer keyboard by using the non-dominant hand. The task consists of repeating a five-element sequence (4-1-3-2-4) as quickly and as accurately as possible for a period of 30 s. To exclude for working memory interference, the numeric sequence (4-1-3-2-4) is displayed on the computer screen for the entire duration of the task. During performance, each key press results in a white dot appearing on the computer screen (below the number sequence), rather than the number itself, so that no accuracy feedback is provided to the subjects.

The session consisted of fifteen 30-s trials with 20-s rest periods between trials. For each trial we measured the number of complete sequences achieved (i.e., speed) and the number of errors made/the number of sequences ratio (i.e., accuracy). The scores (speed and accuracy) obtained in the two final trials were taken as the subject’s “pre-sleep” performance. During the retest post-sleep session, which consisted of four 30-s trials, the averaged scores obtained in the final two trials were taken as the subject’s “post-sleep” performance (the first two trials were considered a subject’s re-adaptation to the task and the scores were not included in the analyses).

**SEEG-EEG data analysis**

Acquisition files were converted to EDF (European Data Format) and analysed by using a software compiled in MatLab (MatLab 7.0, The Matworks, Inc.). This software allowed us to modify montage settings and set filters to the signal. We used a bipolar montage between contiguous electrode contacts and between Fz–Cz scalp electrodes, EOG and EMG derivations. EEG and SEEG channels were 0.33–30 Hz band pass filtered, EOG channel was 0.16–15 Hz band pass filtered, and EMG channel was 5–150 Hz band pass filtered. The same software allowed the scoring of the sleep stages according to standard criteria (Rechtschaffen and Kales, 1968), the removal of artefacts, and the performance of power spectral analysis.

Sleep was scored in 20-s epochs starting from 20 min before the first stage 2 epoch, taking into account scalp EEG, EOG and EMG derivations. During sleep scoring, neocortical and hippocampal SEEG periods with interictal spikes and pathological EEG signals were marked, and removed from the subsequent quantitative analysis. Power spectra were computed by a Fast Fourier Transform routine for 4-s periodograms averaged in 20-s epochs, resulting in a frequency resolution of 0.25 Hz. Frequencies were then collapsed into one 0.5–Hz bin (0.5–1.0 Hz) and 29 1-Hz bins (1.1–30.0 Hz).

For the purposes of this study, for each night (1 baseline and 2 experimental), the SEEG power of the first NREM sleep cycle (stages 2, 3 and 4) and the mean power of the first two REM cycles were taken into account. The first NREM sleep cycle was chosen because of its sensitivity to post-learning plasticity (e.g., Huber et al., 2004), and because it was closer to the experimental manipulation. We averaged the first two REM periods due to the lack of the first REM period in some subjects and inadequate statistical power in the total number of REM sleep epochs during the first cycle. With regard to standard polysomnography, the percentage of NREM sleep stages was calculated on the mean duration of the first cycle, while the REM sleep percentage was calculated on the mean duration of the first two cycles.

Due to a large inter-subject variability on the spike number and distribution and, consequently, on the incidence of rejected epochs across the first NREM cycle, the first NREM cycle was divided into quartiles. This allowed us to compare equivalent sleep periods during the three nights, and to preserve the time-course of each sleep cycle. For each night and quartile the same number of epochs was selected. More specifically, the midpoint of each quartile was identified, and the minimum number of epochs common to all the quartiles was selected around the midpoint. The percentage of rejected epochs in the first NREM cycle for each of the three nights did not differ (F2,14=0.92; p=0.42; mean±SE: baseline: 54.27%±9.17; post-procedural: 62.4%±8.86; post-declarative: 55.26%±10.53). During the first two REM cycles, all the available epochs were selected because of the rare (or absent) epileptic activity in REM sleep.

**Statistical analyses**

Paired Student’s t tests (two-tailed) were performed between pre-sleep and post-sleep performance scores for both memory tasks (PAWT and SFTT). With respect to the polysomnographic data, one-way repeated measure ANOVA with Night (Baseline, Post-declarative learning, Post-procedural learning) as independent factor was carried out separately for each sleep stage (stage 1, stage 2, SWS, and REM).

With regard to SEEG spectral data, given the large variability of power density between patients and between different SEEG derivations, data were normalized for each participant; for each bin, power spectra were expressed as percentages of the total power corresponding to the entire frequency range (0.5–30 Hz). Then, for each bin, we performed a one-way repeated measure ANOVA with Night (Baseline, Post-declarative learning, Post-procedural learning) as independent factor. ANOVAs were performed separately for the first NREM cycle, for the mean REM sleep of the first two cycles, and for cortical and hippocampal derivations. Analyses were corrected for multiple comparisons (Bonferroni). In accordance with the mean correlation between factors (r=0.77), the degrees of freedom (14) and the number of comparisons (120), statistical significance was set at p≤0.017.

**Results**

**Memory tasks**

Patients’ behavioural performances are displayed in Fig. 2. In the PAWT task, patients recalled more word pairs during the retest (morning) trials than during the pre-sleep ones (mean±SE: pre-sleep: 17.37±0.49; post-sleep: 19.12±0.69; p=0.04).

In the SFTT task, the patients’ performance speed was faster during the retest phase (morning) compared to the pre-sleep test, as shown by a tendency towards statistical significance (mean±SE: pre-sleep: 8.75±0.97; post-sleep: 9.81±1.03; p=0.08). No differences were detected with respect to the patients’ accuracy in performing the motor task (mean±SE: pre-sleep: 0.11±0.03; post-sleep: 0.12±0.01; p=0.96).
Percentages of sleep stages in the different nights are reported in Fig. 3. The ANOVA did not reveal significant differences on standard polysomnography at stage 1 ($F_{2,14}=0.77; p=0.48$), stage 2 ($F_{2,14}=2.24; p=0.14$) and REM sleep ($F_{2,14}=0.48; p=0.63$). On the other hand, the ANOVA for SWS reached statistical significance ($F_{2,14}=3.61; p=0.05$): post-hoc comparisons (Fisher PLSD) revealed an increase of SWS during post-procedural learning night compared to both baseline (mean±SE: post-procedural: $35.68±5.96$; baseline: $23.33±7.08$; $p=0.03$) and to post-declarative learning (mean±SE: post-declarative: $23.64±6.38$; $p=0.04$) nights.

**SEEG power spectra**

Overall, sleep SEEG power spectra did not differ between conditions, either for cortical and hippocampal derivations or for NREM and REM periods, except for the hippocampal 0.5–1.0 Hz bin of the post-procedural night. In fact, the one-way ANOVA revealed a significant difference ($p<0.001$) between SEEG power of the P-P and BSL nights.
ANOVAs performed on power spectra revealed a significant difference for the 0.5–1.0 Hz bin power density (F2,14 = 7.39; p = 0.006) selectively. This difference was observed only for the hippocampal derivation during the first NREM cycle (see Fig. 4). Post-hoc comparisons revealed that 0.5–1.0 Hz bin power density was significantly higher during post-procedural learning night compared to the baseline night (mean±SE: post-procedural: 23.69±0.97; baseline: 21.39±1.04; p = 0.001). Power density in the same frequency bin during the post-declarative learning night was not statistically different from both baseline and post-procedural learning nights, showing an intermediate value (mean±SE: post-declarative = 22.31 ± 1.27).

Since previous scalp EEG studies reported a relation between learning and EEG power increase in the delta band (Huber et al., 2004, 2007), we performed a further analysis taking into account the whole delta range (0.5–4.0 Hz). This ANOVA confirmed a significant difference between nights (F2,14 = 4.47; p = 0.03; mean±SE: baseline: 18.66±0.64; post-declarative: 18.95±0.58; post-procedural: 19.28±0.51). However, the effect was strictly dependent on modifications in the very low frequency range. In fact, the same ANOVA carried out on the 1.1–4.0 Hz range (i.e., excluding the slow oscillation range) did not result significant (F2,14 = 0.05; p = 0.95).

Correlations between performance improvement and SEEG power spectra

We performed a correlation analysis (Pearson’s r) to evaluate the possible relationship between the magnitude of SFTT performance improvement (differences between post- and pre-sleep procedural performance speed) and the changes in the SEEG hippocampal low frequencies (difference between experimental and baseline nights). The results showed a significant correlation between procedural performance improvement and SEEG power in the lowest frequency bin (0.5–1.0 Hz; r = 0.70, p = 0.05; see Fig. 5). The correlation with the delta band (1.1–4.0 Hz) power did not reach statistical significance (r = 0.59, p = 0.12).

Discussion

In the present study we reported the first local effects of declarative and procedural learning on sleep as recorded from both scalp and intracranial derivations. We showed that a short, but intensive, training on a sequential finger tapping task is followed by an increase in the amount of scalp recorded SWS, as well as hippocampal SEEG power in the very low frequency range (0.5–1.0 Hz) during the first post-learning NREM period. We also found that the magnitude of procedural performance improvement is significantly correlated with the subsequent SEEG low frequency power increase, which supports the existence of a direct link between procedural memory consolidation and very low hippocampal SEEG rhythms.

In a previous study, an enhancement of delta EEG power has been reported after intensive training in performing a motor task; such increase was localized in the specific cortical area involved in performing the task (Huber et al., 2004). This result was interpreted as supporting the synaptic homeostasis hypothesis, in which the plastic processes occurring during wakefulness are suggested to result in a net increase in synaptic strength in many brain circuits (Tononi and Cirelli, 2003, 2006). According to this hypothesis, sleep, more specifically slow oscillations, would contribute to synaptic consolidation (or produce synaptic downscaling) and increase signal-to-noise ratio in relevant neural circuits. Although data regarding the specific effects of learning on sleep recorded from subcortical structures were not available prior to the present study, it was legitimate to hypothesize that the hippocampus should have obeyed the same mechanisms already observed in the neocortex. Indeed, recent analyses revealed that sleep in the hippocampus shares some basic characteristics with the well-known scalp recorded sleep (Moroni et al., 2007). Accordingly, parallel molecular changes have been recently found in both the cerebral cortex and the hippocampus, as shown by molecular correlates of synaptic potentiation (during wakefulness) and depression (during sleep) being similar in these two forebrain areas (Vyazovskiy et al., 2008).

Thus, the increase of power in the very low frequency range observed in our study may reflect the need of the hippocampal neurons to regain the synaptic balance altered by pre-sleep learning. At variance with previous scalp EEG studies (Huber et al., 2004, 2007), the effect was limited to, and strictly dependent on, the very low frequency range (0.5–1.0 Hz). A reasonable explanation for this different findings may rely on the functional dissociation that has been recently observed in the delta band during hippocampal sleep (Moroni et al., 2007). If this is the case, very low frequencies may reveal an independent behavior in the hippocampus compared to the neocortex. Therefore, within the hippocampus, the effects of plasticity on sleep may be limited to the very low frequencies rather than the entire delta range. This is consistent with the stimulation paradigms of hippocampal cells in vitro, showing that stimulations at less than 1 Hz are ideally suited to induce depotentiation or depression of synaptic transmission (Kemp and Bashir, 2001). Remarkably, in humans, it has been recently found that, within the delta frequency range, the lowest frequencies (0.75–1.0 Hz) show the highest correlation with the overnight improvement in a different procedural (texture discrimination) task performance (Aeschbach et al., 2008).

One interesting and unexpected result of our study is the lack of any (predictable) effect of declarative learning on the hippocampal sleep features. One may note, however, that although the involvement of the hippocampal structure in the episodic-declarative memory formation is undisputed (for a review, see Squire et al., 2004), recent evidence supports the role of the hippocampus and related cortex in...
both implicit and explicit sequence learning (Poldrack and Rodriguez, 2003; Schendan et al., 2003). Moreover, sleep dependent plastic modifications of the hippocampal activation have been reported after learning of the identical task used in our study (Walker et al., 2005). These data provide evidence supporting the role of the hippocampus in the formation of higher order associations under both implicit and explicit sequence learning, possibly in the ordering of the individual motor elements in a correct temporal series. Such involvement may be responsible for the need of rearranging, during sleep, the balance of synaptic weight in this specific brain structure.

In contrast with the findings described above, a recent fMRI study on cerebral plasticity after learning of a list of paired words (the same declarative task used in our study) (Gais et al., 2007), reported that the hippocampus was not the main site of activity during either learning or recall. This low hippocampal activation may be explained by the stimulus words included in the task, which were already well represented in memory. Moreover, word pairs were already semantically related, which might have reduced further the strength of the hippocampal activity. Since hippocampal activation has been reliably correlated with effective memory formation only for those stimuli that were encoded in a relational manner (Davachi and Wagner, 2002), the hippocampal involvement relative to semantic processing of the words could have been of minor importance.

A further reason for the lack of effects of declarative learning on hippocampal sleep may be related to the existence of functional differences within the hippocampal formation. Recent neuroimaging studies have shown that anterior and posterior hippocampus could be more involved, respectively, in implicit vs explicit sequence learning (Schendan et al., 2003), in the encoding of verbal-semantic vs visuospatial material (Parsons et al., 2006) in episodic memory encoding vs retrieval (Lepage et al., 1998) and in the formation vs the use of a cognitive map (Iaria et al., 2007). Such functional differentiation, however, is still debated, and needs further elucidation. Nevertheless, given the reduced sample size and the diversity of anatomical localizations (see Table 1), it is not possible to weigh and rule out the net contribution of anatomical factors to the present results. In a similar vein, the heterogeneity of neocortical recording sites (Table 1) may be responsible for the lack of effects of the experimental manipulations on cortical SEEG power in the low frequencies that we observed in our study. Indeed, it is well recognized that scalp recorded delta EEG power shows large regional differences during sleep (Werth et al., 1997; Ferrara et al., 2002), and that the effects of learning on this band is localized to the cortical areas directly involved in the learning task (Kattler et al., 1994; Huber et al., 2004). Similarly, SEEG recordings sampled from different neocortical areas do strikingly differ at visual analysis (data not shown). This observation is confirmed by the spectral analysis of SEEG power in the very low frequency range recorded from frontal derivations (patients # 1 and # 5, Table 1): these data show different power values and distribution across nights (mean±SE: baseline: 38.52±2.60; post-declarative: 41.82±6.40; post-procedural: 39.10±10.66) compared to that sampled from more posterior sites (precuneus, patients # 6 and # 8; mean±SE: baseline: 58.83±10.17; post-declarative: 58.17±13.96; post-procedural: 58.25±9.08). Future studies involving large samples of patients with homogeneous neocortical locations could shed more light on the relations between learning and local homeostasis of the low EEG frequencies during intracortically recorded sleep.

Our findings also raise the question of whether the increase in hippocampal low frequencies is a specific and local phenomenon, or is the product of a global increase of slow waves. However, the lack of any significant difference between the three nights in the Hz by Hz cortical SEEG power spectra and scalp recorded EEG (data not reported) strongly supports the interpretation of a specific hippocampal effect.

In summary, in this study we reported an increase of hippocampal SEEG power in the very low frequency range (0.5–1.0 Hz) during the first NREM period immediately following procedural learning. This finding can be interpreted according to the synaptic homeostasis hypothesis (Tononi and Cirelli 2003, 2006): hippocampal slow oscillations during sleep, with the characterized sequence of depolarization (up-phase) and hyperpolarization (down-phase) at the cellular level, may be associated with the local processes of post-learning synaptic downscaling. Future studies including larger samples of participants may overcome the limitations we encountered in our study, such as the differences in the anatomical localization of the deep electrodes across patients.

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