Interpretation of the Intracranial Electroencephalogram of the Human Hippocampus

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KEYWORDS

• Epilepsy • Epilepsy surgery • Intracranial EEG • Hippocampus

KEY POINTS

- Understanding what constitutes an abnormal feature/pattern in the intracranial electroencephalogram (iEEG) is inherently linked to the understanding of its normal constituents.
- Stereo-electroencephalography (sEEG) contacts in hippocampal space are picking up the surrounding neuronal activity with finer spectral detail, due to the lack of major white matter filtering.
- sEEG contacts in the hippocampus record high-amplitude surrounding neuronal activity due to a combination of strong electric fields in the transverse and anterio-posterior directions.
- Intermittent delta activity in the hippocampal iEEG is a normal property and should not be interpreted as a marker of hippocampal epileptogenicity or other pathologic condition.
- Near-continuous delta, lack of higher frequencies in the background, reduced foreground spindles and barques, and interictal activity abundance, constitute hallmarks of abnormal hippocampal iEEG.

INTRODUCTION

Stereo-electroencephalography (sEEG) allowed epileptologists and neurophysiologists in the epilepsy field to record the intracranial electroencephalogram (iEEG) from regions of the human brain previously unreachable by subdural electrodes.[1] The most recent introduction of robotic technology in the operating room setting, along with the development of multimodal imaging platform for surgical planning, has further increased the accuracy of sEEG targeting.[2,3] Our experience from studying nonepileptic regions of the human brain has revealed that not all brain structures generate the same iEEG because their spectral constituents differ across regions and brain states.[4–6] Consequently, the interpretation of the iEEG signal derived by sEEG requires individualized approaches, depending on the anatomic structure being recorded.[7–9]

In this article, the main aspects for the interpretation of the hippocampal iEEG will be presented, namely normal background features and foreground elements, as well as characteristics of the abnormal background of the hippocampus because of established epileptogenicity. A special paragraph will be devoted to the notably increased amplitude of the hippocampal iEEG, which may render some foreground iEEG elements more aggressive than they actually are. The terms "sEEG" (implemented by depth electrodes) and "electrocotricography" ("ECoG"; implemented by

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subdural grid and strip electrodes) will be used hereby as subcategories of the broader term "iEEG" because they constitute distinct modalities of recording the intracranial electric fields of the brain.[10]

INTERPRETATION OF THE HIPPOCAMPAL INTRACRANIAL ELECTROENCEPHALOGRAM

Understanding the Intracranial Electroencephalogram Amplitude in the Hippocampus

In his classic '85 article, Pierre Gloor described the manner in which synchronized population pyramidal neuron-generated postsynaptic potentials give rise to electric fields of different orientations depending on their position across the gyral-sulcal continuum.[11] Modeling the neuronal sources that generate the ECoG signal, he described how the disk-shaped subdural electrode contacts placed on the cortical surface are primarily sensitive to electric fields of the gyral crown. This is due to the vertical orientation of the electric fields to the electrode contact surface. He also described that the subdural electrode disks are secondarily sensitive to electric fields generated in the sulcal walls and minimally sensitive to electric fields originating toward the bottom of the sulci. As such, the subdural ECoG signal is primarily representing activity of neocortical gyral surface, with mild representation of sulcal activity. Because the subdural iEEG approach has been the dominant in the twentieth century, the epilepsy surgery community is familiar with the above concept.[12] However, as sEEG has progressively spread worldwide only since the first 2 decades of the twenty-first century, it is imperative to understand the respective neuronal contributions to the iEEG signal in order to provide clinically meaningful interpretations.

The distinct geometry of sEEG electrodes and their contacts renders the acquired signal also distinct from the subdural electrode-derived ECoG signal in terms of neocortical representation. Understanding the geometry of iEEG recording by both subdural and sEEG electrodes is the first step in understanding the neuronal distribution represented by each recording modality. Because the subdural disk electrodes are primarily sensitive to vertical electric fields in a single-dimension fashion, the cylindrical shape of the sEEG electrode contacts render them sensitive to vertically oriented electric fields but in a 2-dimensional fashion (2D). In other words, although subdural contacts are optimally picking up the neuronal activity of the surface they are placed on, sEEG contacts are optimally sensitive to proximal electric fields generated at the same horizontal plane all around each contact.[13] The volume of a subdural grid provides a multiplicity of 1-dimensional ECoG recording points, thereby generating a 2D overview of the brain's electrical activity. The multiple contacts of a single sEEG electrode provide a multiplicity of 2D recording planes, thereby allowing for a 3-dimensional (3D) overview of the electrical activity throughout the surrounding brain; a 3D representation enhanced by the presence of multiple sEEG electrodes.[14–18]

Because of the geometric differences, the iEEG signal recorded by a sEEG electrode going through a neocortical gyrus (**Fig. 1**A, B) represents a different portion of the gyral electric activity compared with the iEEG recorded by a subdural electrode on the same gyrus. A subdural electrode at the top of the gyrus is highly sensitive to synchronized neuronal activity representing cortical-subcortical interaction (mainly neocortical layers 5 and 6), which generate electric fields of vertical orientation with respect to the gyral surface.[11] However, the sEEG signal at the gyral crown is more sensitive to synchronized neuronal activity generated at the entry point plane that represents cortico-cortical interactions (primarily neocortical layers 2, 3, and 4) because they generate electric fields of vertical orientation to the cylindrical surface of the sEEG contacts[13] (see **Fig. 1**B). However, as the cortico-cortical interaction can create electric fields of opposite direction, the iEEG signal at the horizontal gyral plane is prone to cancellation among surrounding neuronal populations, thereby rendering the sEEG signal of lower amplitude than that of a subdural disk where most neuronal populations generating the ECoG signal have the same orientation. Further contribution to the sEEG signal comes from electric fields generated from the walls and the bottom of the surrounding sulci (see **Fig. 1**A). These electric fields can represent both cortico-subcortical and cortico-cortical interactions depending on the orientation of the wall and the bottom with respect to the sEEG electrode; the deepest their generator neuronal populations reside, the more unlikely they can be picked up by a surface subdural contact. However, the volume of white matter that often resides between the sEEG contacts and the neocortical generators is a confounding factor that affects the amplitude as well as the content of the recorded iEEG signal.[19] A sEEG electrode passing in parallel but distant to a sulcal wall will record an iEEG signal of lower amplitude and poorer in high-frequency content than one that passes close to the inner surface of the sulcus wall. For that reason, one of the main goals of sEEG implantation planning is to increase the

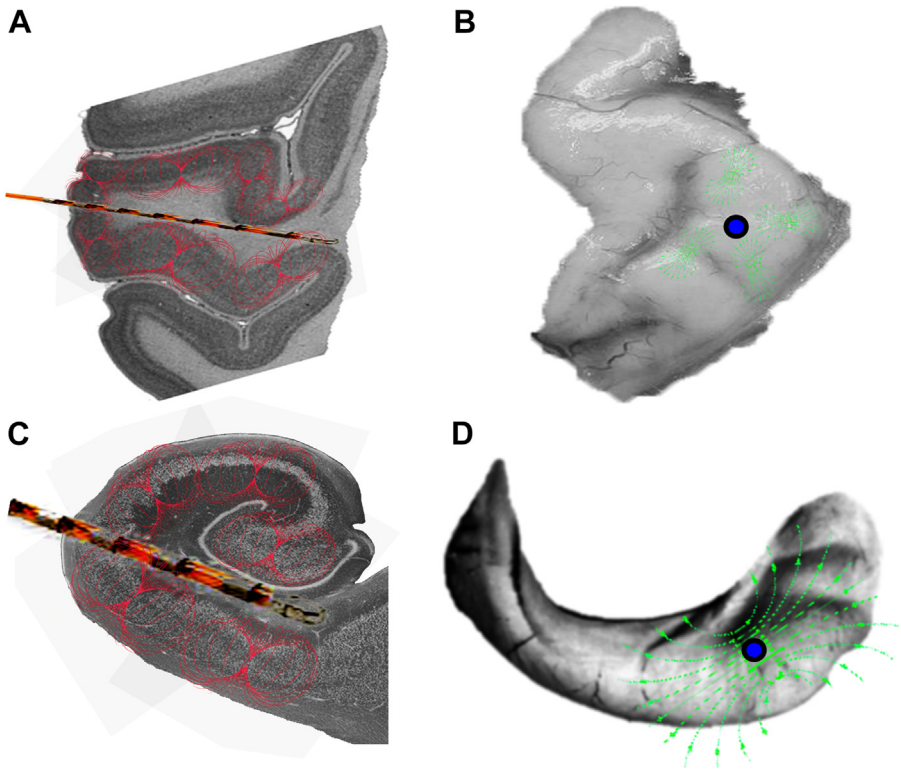

Fig. 1. Electric fields in neocortex and archicortex architectures. (*A*) An sEEG electrode passing through a hemispheric gyrus (coronal section) is recording moderate neocortical activity from the gyral crown entry point. The sEEG contacts are picking up vertically oriented electric fields from the proximal walls of the 2 adjacent sulci, although the signal is often high-passed filtered because of the white matter residing in between. The red isoelectric lines represent fields generated along the cron and the walls of a typical neocortical gyrus. (*B*) The main electric fields that constitute the sEEG signal at the entry point (lateral cortical view) are generated by cortico-cortical connections. However, although these electric fields are vertical to the cylindrical sEEG surface, they can be opposing in direction and partially cancel each other because of the multidirectional neocortical connections, thereby resulting in an overall moderate-amplitude neocortical sEEG signal. The green isoelectric lines represent fields generated across the neocortical surface because of cortico-cortical interactions. (*C*) An sEEG electrode passing through the hippocampal parenchyma (coronal section) is picking up more immediate neuronal activity due to its increased proximity to the trisynaptic circuit constituent regions (CA1–4 and dentate gyrus) and the reduced white matter (mossy fibers) volume around it. The red isoelectric lines represent fields generated along the transverse cross-section of the hippocampus. (*D*) In addition to the electric fields in the transverse axis, sEEG contacts implanted in the hippocampus also pick up high amplitude unidirectional electric fields forming across longitudinal networks of the CA1 and CA3 regions (lateral view of the hippocampal surface). The green isoelectric lines represent fields generated across the longitudinal axis of the hippocampus.

number of contacts passing through or very close to gray matter structures on their way to their target. Overall, the combination of the above confounding factors, that is, the electric field cancellations at the gyral crown and the parenchymal white matter that surrounds the sEEG electrode, result in an iEEG signal of moderate although fair amplitude and often appearing as low-pass filtered.

It is clear that the geometric features of the brain parenchyma surrounding the sEEG electrodes play a significant role in the iEEG signal recorded, in terms of both quality and anatomic representation. It is thereby conceivable that the archicortical densely folded 3-layered environment of the hippocampus will result in an iEEG signal of different qualitative and quantitative features compared with the 6-layered sparsely folded neocortical structures. Indeed, the iEEG from sEEG electrodes residing in hippocampal space presents with high amplitude and wide frequency range (toward both lower and higher frequencies), thereby overshadowing the rest of the nonhippocampal contacts of the implantation coverage when looking at the full reviewing montage. There are 2 reasons for the distinct hippocampal sEEG signal: (1) the dense folding of the hippocampal CA1-4 regions

and the dentate around the hilus space and the mossy fibers allow for the sEEG contacts to pick-up the adjacent neuronal electric fields of the transverse trisynaptic circuit[20] from a closer proximity, without major white matter interference (Fig. 1C) and (2) the longitudinal connections across the long axis of the hippocampus, formed between neurons of the CA1 and CA3 regions separately,[21–25] generate strong unidirectional noncanceling electric fields of vertical direction to the traditional orthogonal trajectory of sEEG electrodes implanted in the hippocampus (Fig. 1D). As a result, sEEG contacts in hippocampal space are picking up the surrounding neuronal activity with finer spectral detail, due to the lack of white matter filtering, and higher in amplitude, due to receiving a combination of strong electric fields in the transverse and anterio-posterior directions. In addition, from a neurophysiological standpoint, the sEEG signal represents 2 seemingly independent hippocampal circuits, the trisynaptic and the longitudinal CA3/CA1 networks.

The high amplitude of the hippocampal sEEG signal may bias the iEEG interpretation toward interictal epileptic activity and archicortical epileptogenicity. The recommendation for a balanced review is to reduce the amplitude of the individual contacts that reside in the hippocampal parenchyma (because they are determined by the post-implantation CT fused with a preoperative MRI) so as their background iEEG level is comparable to that of the lateral temporal neocortical contacts of the same electrode (typically a 3 or 4 times reduction is sufficient). Moreover, note that before interpreting the hippocampal iEEG, the presence of the sEEG contacts in the hippocampal parenchyma has to be verified by an accurate 3D electrode reconstruction; a low amplitude iEEG, lacking the variety of high-frequency features, may suggest that the sEEG electrode intended to record from the hippocampus failed to reach its target.

The Normal Intracranial Electroencephalogram Background of the Hippocampus

There is only a handful of studies investigating the normal profile of the iEEG of the human hippocampus, despite the fact that sEEG has been used to target the mesio-temporal structures for more than 70 years. The consistent presence of beta oscillatory activity in the hippocampus has been confidently established,[26] as well as the occasional presence of gamma.[27] The presence of prominent, although irregular, delta and theta activities in the hippocampus has been reported by early iEEG recordings.[28] More recently, an individual peak in the low-delta range has been found to render the iEEG power profile of the hippocampus unique compared with the rest of the brain during wakefulness.[4,6] Interestingly, the hippocampus presents with reduced alpha oscillations compared with the rest of brain throughout the sleep–wake cycle.[6]

The iEEG of the hippocampus has been found to be reactive to simple tasks of relaxed wakefulness, with the background theta and delta power found to be increased when patients kept their eyes closed in comparison with the eyes open state.[29] Task-specific reactivity of the hippocampal iEEG background was also reported. Engagement in a visuospatial task resulted in decrease in background theta and delta activities, whereas the performance of a verbal task increased the power in both bands.[29,30] Tasks requiring the emergence of spatial navigation skills have been associated with the presence of ~3 Hz rhythmic activity in the human hippocampus.[31] Results such as these have demonstrated that the spectral content of the hippocampal background iEEG can be state-dependent and task-dependent; however, in the presurgical setting of the epilepsy monitoring unit such interpretations are difficult to be made, despite the presence of simultaneous video.

During sleep, the prominence of delta activity persists in the hippocampus throughout the non–rapid eye-movement (NREM) phase.[32] A detailed whole-brain study of iEEG spectral profiles across the sleep stages showed that the hippocampus presents with significant power peaks in the mid-delta range during NREM II and slow wave sleep (SWS).[5] The overall dominance and stability of hippocampal delta during NREM sleep is significant, considering that the iEEG in rest of the temporal lobe becomes progressively slower as the sleep deepens.[6] This phenomenon suggests that the level of sleep deepening has a higher limit in the archicortex than the surrounding neocortex. In other words, the hippocampus is maintaining a steady level of sleep, lighter than that of the neocortex during SWS. A similar counterintuitive phenomenon was observed during rapid eye-movement (REM) sleep, where the hippocampus also presents with increased delta power.[5,33,34] This finding was interpreted in the context of the hippocampus belonging to a group of brain regions (namely the primary visual, auditory, and motor regions) that do not share the cortical high-frequencies and mixed-frequencies iEEG profile brought on by the emergence of REM.[35] Another interesting observation is that theta activity during REM seems rather reduced compared with wakefulness—a feature not observed in the

rest of the brain.[35] These findings reveal an iEEG sleep profile of the hippocampal archicortical formation that is distinct and independent from the concurrently manifested neocortical one. A typical sample of normal iEEG from a patient with a nonepileptogenic left hippocampus (Fig. 2) during NREM II is shown in Fig. 3.

It is also important to note that although focal delta activity has been typically associated with underlying focal brain lesions,[36,37] its presence in the hippocampal iEEG has been demonstrated to be a normal property and should not be interpreted as a marker of hippocampal epileptogenicity or other pathologic condition.

The Normal Intracranial Electroencephalogram Foreground Elements of the Hippocampus

The hippocampal spindles

The presence of spindles in the hippocampus has been reported since the first intracranial recordings in epilepsy patients.[28] Despite the fact that they were given their name due to their morphologic similarity with the sleep spindles recorded on scalp EEG—they are both waxing and waning sinusoidal oscillations—studies have shown that they occur independently.[38,39] In other words, there is no temporal correlation between the spindles generated in the archicortex of the hippocampus and the spindles appearing on scalp EEG during NREM sleep intervals; apparently, the latter are paced by thalamo-cortical interactions.[40] Therefore, it is recommended that we refer to the spindles of the hippocampal iEEG as "hippocampal spindles," so to avoid confusion with their scalp doppelgangers. Hippocampal spindles, being exclusively generated in hippocampal space, are spatially restricted in the brain compared with the scalp sleep spindles that seem more diffuse,[39] and typically oscillate at 12 to 13 Hz.[5] The hippocampal spindles constitute a normal element of the hippocampal iEEG because they are met rather equally in epileptogenic and nonepileptogenic hippocampi, at percentages of ~90% and ~80%, respectively.[41] However, their frequency of occurrence in the iEEG background can be reduced inversely proportionally to the increase of interictal activity in epileptogenic hippocampi.[42] Hippocampal spindles are not specific to either the left or the right hippocampus, and they can manifest both independently and at times in synchrony between the 2 hippocampi.[41] An example of background iEEG with prominent hippocampal spindle activity is shown in Fig. 4.

The hippocampal barques

Hippocampal barques are the intracranial correlate of the well documented "14&6/sec positive spikes" normal variant that appears on scalp EEG.[43,44] They manifest as series of high-amplitude ~14 Hz spikes following a "'ramping-up/often ramping-down" profile that may be overlaid on lower amplitude ~6 Hz slow waves. Three barque subtypes have been identified: (1) The 14 Hz-only subtype that presents as a series of 14 Hz high-amplitude spikes; (2) The mixed 14 and 6 Hz subtype that presents as a series of 14 Hz high-amplitude spikes overlaid by 6 Hz slow waves or followed by 6 Hz spike-over-slow wave complexes; (3) The 6 Hz-only subtype that manifests as a series of 6 Hz high-amplitude spike-over-slow wave complexes (Fig. 5).[41,44] Although they manifest with negative polarity within the hippocampus parenchyma, they reverse their phase outside the hippocampal volume to positive, thereby generating the positive spikes

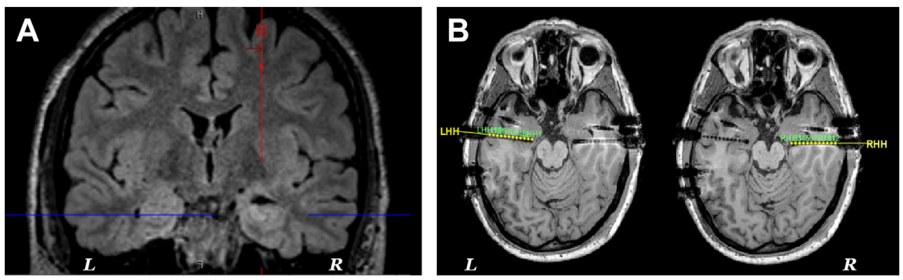

Fig. 2. A patient with temporal lobe epilepsy who underwent bilateral temporal sEEG to establish laterality of seizure origin. (*A*) Coronal FLAIR section showing hyperintensity in the right hippocampal region. (*B*) sEEG electrode reconstruction over a postoperative T1. The left (LHH) and right (RHH) sEEG electrodes implanted in an orthogonal fashion from the middle temporal gyrus targeting the respective hippocampi in the anterior/head region (LHH: left hippocampus head; RHH: right hippocampus head). This intracranial investigation confirmed the potential of the right hippocampus to generate the typical seizures of the patient, and showed no ictal involvement of the left hippocampus. The iEEG samples shown in the following Figs. 3–6 are derived from this sEEG investigation.

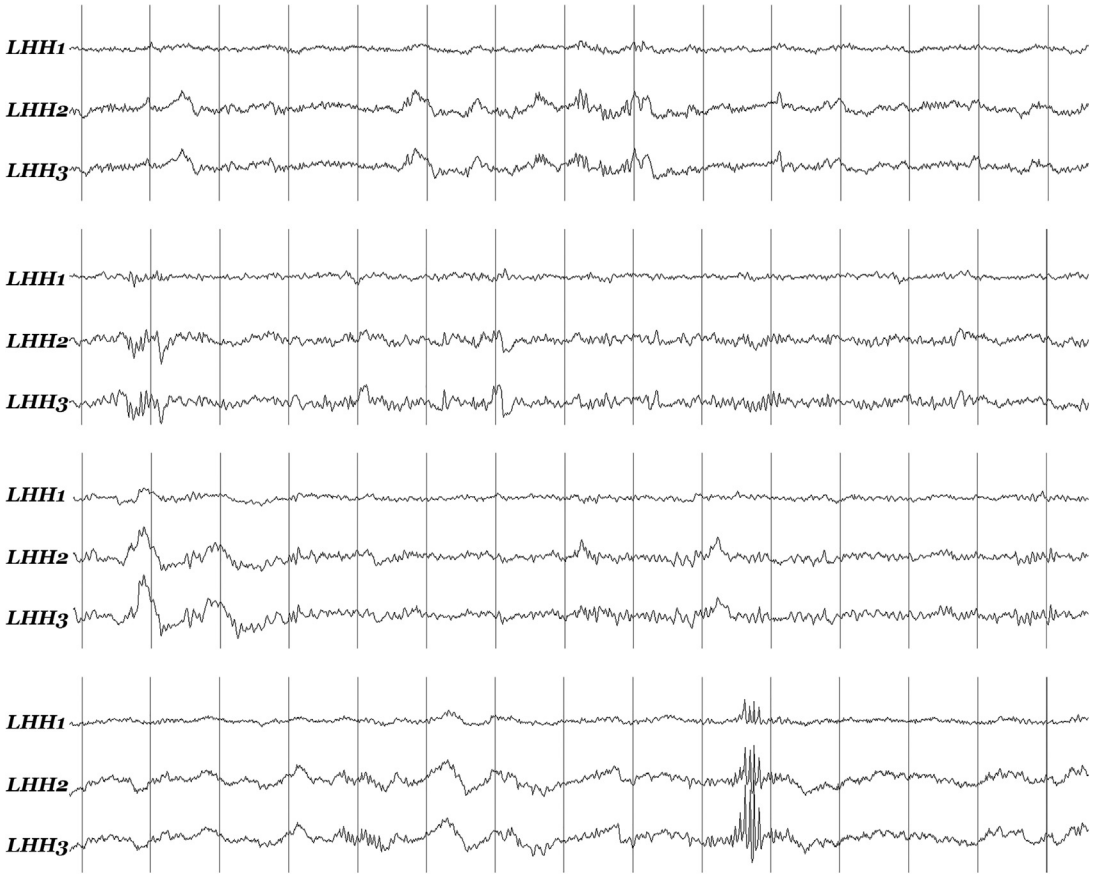

Fig. 3. Typical normal hippocampal iEEG sample from the nonepileptogenic anterior left hippocampus of our Fig. 2 patient during NREM II stage of sleep (4 consecutive intervals of 15 s each, total 1 min). Contacts 1 to 3 were in the anterior hippocampus parenchyma. Note: (1) The intermittent and prominent background delta activity, manifesting with either moderate-amplitude prolonged delta wave sequences or high-amplitude brief delta waves. (2) The high frequencies, mostly in the beta range, constantly present in the hippocampal iEEG background, often overlaying intermittent delta waves. (3) The frequent occurrence of hippocampal spindles. (4) The occasional occurrence of hippocampal barques. Vertical lines represent 1-s intervals. The montage is referential to a midline scalp electrode.

profile of their scalp 14&6/sec manifestations.[45] Their high-amplitude spiky morphology has often been the reason that barques have been misinterpreted as paroxysmal (Fig. 6; barque activity in the nonepileptogenic left hippocampus can be interpreted as polyspike activity), and thereby as markers of hippocampal epileptogenicity, in the past.[46,47] However, the hippocampal barques, similar to hippocampal spindles, are normal variants of the hippocampal iEEG because they occur rather equally in epileptogenic and nonepileptogenic hippocampi, at percentages of ~20% and ~35%, respectively, with the higher incidence in the latter suggesting a tendency to increase their presence in the absence of epileptogenic substrates.[41] Barques manifest either exclusively or with higher amplitude in the posterior hippocampus.[45] Hippocampal barques occur predominantly, although not exclusively, during NREM II and SWS stages of sleep, with rare to occasional occurrences in NREM I and REM sleep stages, as well as the wakefulness state. Interestingly, hippocampal barque density (count per minute) can be found increased during SWS compared with NREM II (Kokkinos et al., 2023, unpublished data).

As spindles and the 14 Hz-only barque subtype can share the same spectral content and assume similar morphologies, 3 criteria were developed to tell them apart: (1) Amplitude: Barques present on iEEG with moderate-amplitude to high-amplitude profiles while spindles present with low-amplitude to moderate-amplitude profiles; the amplitude criterion has only within-patient

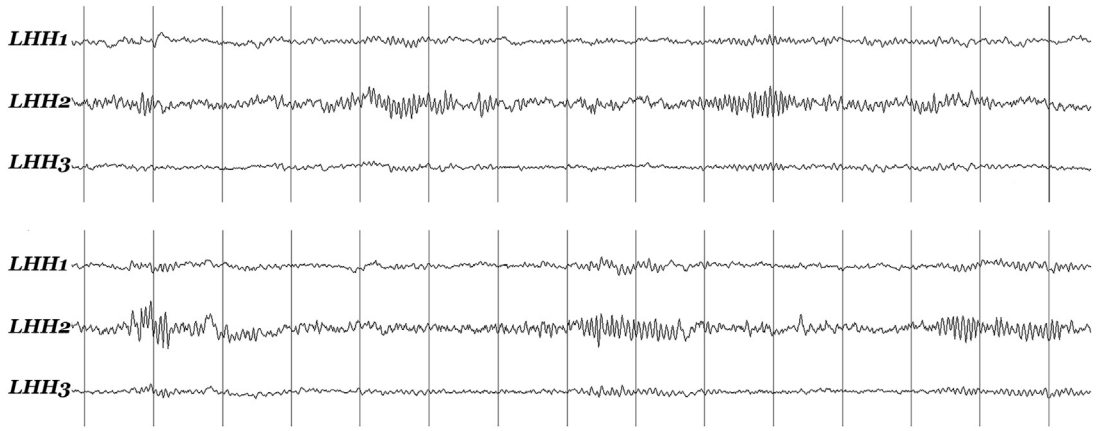

Fig. 4. Normal hippocampal iEEG sample of prominent spindle activity from the nonepileptogenic anterior left hippocampus of our Fig. 2 patient during NREM II stage of sleep (2 consecutive intervals of 15 s each, total 30 s). Note that hippocampal spindles can be brief (<1 s) or prolonged (>1 s), often overlaid on slow delta/theta waves and occur every 4 to 6 s. Vertical lines and montage as in Fig. 3.

validity due to the high variability of hippocampal iEEG waveform amplitudes across subjects because of respective variability in sEEG contact locations and impedances. (2) Symmetry: Barques are highly asymmetric waveforms, with a high-amplitude negative phase and a moderate-amplitude to low-amplitude positive phase, whereas spindles are relatively symmetric as sinusoidal oscillations. (3) Paroxysmality: Barques manifest as spiky waveforms, whereas spindles are rather smooth/blunt sinusoids.

The Abnormal Background Intracranial Electroencephalogram of the Hippocampus

Understanding what constitutes an abnormal feature/pattern in the iEEG is inherently linked to the understanding of its normal constituents. Although there have been no focused studies investigating the abnormal features of the hippocampal background iEEG, some empirical observations are hereby outlined, based on our current knowledge of the hippocampus' normal background iEEG properties.

1. An iEEG background with abundant, near-continuous or continuous delta wave activity, that may or may not be rhythmic, is more likely to be abnormal. As described previously, delta activity is prominent in the hippocampus but is mostly intermittent, allowing for iEEG intervals of higher frequency profile (such as the interval with hippocampal spindle predominance of Fig. 4).
2. An iEEG background lacking high-frequency components, such as transient and/or irregular low-amplitude elements in the beta and low gamma range, and thereby presenting as a suppressed iEEG background, is more likely to be abnormal. The normal background, as one can tell from the samples of Figs. 3 and 4, is rich in low-amplitude mixed frequencies of variable duration and distribution.

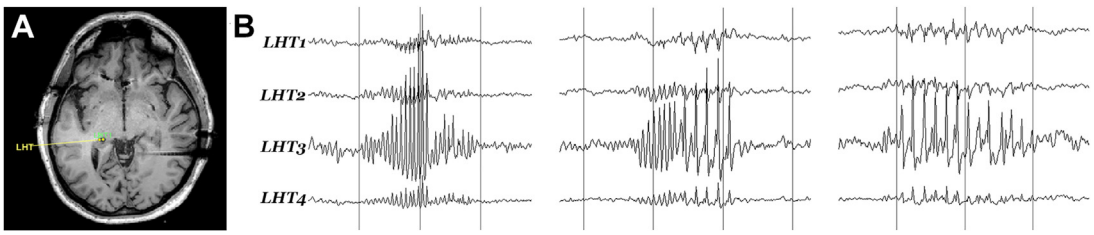

Fig. 5. Short samples of normal hippocampal iEEG demonstrating the 3 barque subtypes from the nonepileptogenic posterior left hippocampus of our patient in Fig. 2. (*A*). Barques are best recorded from the tail of the hippocampus (LHT: left hippocampus tail). (*B*) Left: The 14 Hz-only subtype that presents as a series of 14 Hz high-amplitude spikes; Middle: The mixed 14 and 6 Hz subtype that presents as a series of 14 Hz high-amplitude spikes overlaid by 6 Hz slow waves or followed by 6 Hz spike-over-slow wave complexes; Right: The 6 Hz only subtype that manifests as a series of 6 Hz high-amplitude spike-over-slow wave complexes. Vertical lines and montage as in Fig. 3.

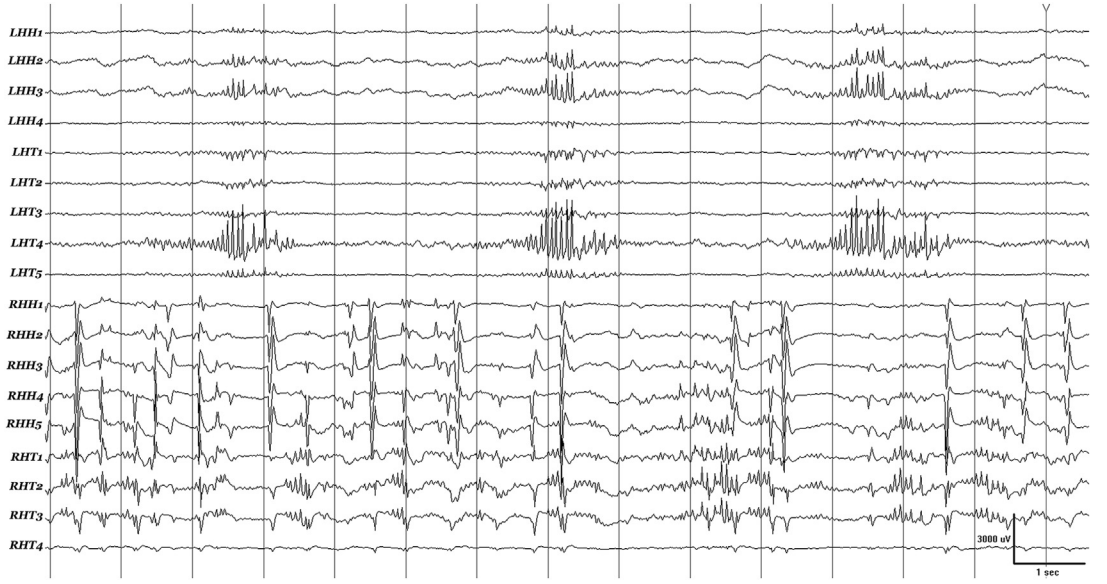

Fig. 6. Bilateral hippocampal iEEG from the patient of Fig. 2, with each hippocampus targeted in the anterior/head and the posterior/tail regions (LHH: left hippocampus head; LHT: left hippocampus tail; RHH: right hippocampus head; RHT: right hippocampus tail). The series of hippocampal barques, maximum in the left hippocampus tail (LHT1-5), can be easily misinterpreted as paroxysmal activity, namely polyspikes. The abundance of interictal spiking activity in the right anterior hippocampus (RHH1-5) is overwhelming the iEEG background and renders it hardly appreciable. The tail of the right hippocampus (RHH1-4) presents with mixed local barque/spindle activity and propagated interictal spikes from the ipsilateral anterior hippocampus. Note that the interictal activity of the sclerotic and epileptogenic right hippocampus does not infiltrate the iEEG of the nonepileptogenic left hippocampus.

3. An iEEG background lacking or presenting with notable reduction in distinctive foreground elements, such as hippocampal spindles and/or barques, is more likely to be abnormal. The occurrence of hippocampal spindles has been shown to be inversely affected by the volume of interictal activity during sleep,[42] and hippocampal barques appear less often in the epileptogenic hippocampal population.[41]
4. An iEEG background overwhelmed by interictal activity to the degree that the background itself is hardly discernible and appreciable, is most likely abnormal (see the right hippocampus of Fig. 6). In contrast, transient and irregular interictal activity recorded in the hippocampus can be interpreted because of inherent epileptogenicity but could also be the result of its pivotal networking connectivity to temporal and extratemporal structures that propagate epileptic activity; in both cases, the iEEG background can be reasonably appreciated and the interictal activity recorded does not constitute a definite marker of hippocampal epileptogenicity.

Note that 2 and 3 can be a result of the sEEG electrode missing the hippocampus and residing either in ventricular space or white matter space surrounding the hippocampus. It is imperative that electrode and contact locations are verified in the hippocampal parenchyma by accurate 3D electrode reconstruction for a confident and meaningful iEEG interpretation to be carried out.

SUMMARY

Understanding what constitutes an abnormal feature/pattern in the iEEG is inherently linked to the understanding of its normal constituents. The sEEG contacts in hippocampal space are picking up the surrounding neuronal activity with finer spectral detail, due to the lack of major white matter filtering. Moreover, the sEEG contacts in the hippocampus record high-amplitude surrounding neuronal activity due to a combination of strong electric fields in the transverse and anterioposterior directions. Intermittent delta activity in the hippocampal iEEG is a normal property and should not be interpreted as a marker of hippocampal epileptogenicity or other pathologic conditions. Hippocampal spindles and barques are normal constituents of the hippocampal iEEG foreground activity. However, a constellation of near-continuous delta, lack of higher frequencies in the background, reduced foreground spindles

and barques, and interictal activity abundance, constitute hallmarks of an abnormal hippocampal iEEG.

DISCLOSURE

The author has no conflict of interest to disclose.

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