ORIGINAL ARTICLE

Increased delta power as a scalp marker of epileptic activity: a simultaneous scalp and intracranial electroencephalography study

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Abstract

Background and purpose: The purpose was to evaluate whether intracranial interictal epileptiform discharges (IEDs) that are not visible on the scalp are associated with changes in the frequency spectrum on scalp electroencephalograms (EEGs).

Methods: Simultaneous scalp high-density EEG and intracranial EEG recordings were recorded in nine patients undergoing pre-surgical invasive recordings for pharmaco-resistant temporal lobe epilepsy. Epochs with hippocampal IED visible on intracranial EEG (ic-IED) but not on scalp EEG were selected, as well as control epochs without ic-IED. Welch's power spectral density was computed for each scalp electrode and for each subject; the power spectral density was further averaged across the canonical frequency bands and compared between the two conditions with and without ic-IED. For each patient the peak frequency in the delta band (the significantly strongest frequency band in all patients) was determined during periods of ic-IED. The five electrodes showing strongest power at the peak frequency were also determined.

Results: It was found that intracranial IEDs are associated with an increase in delta power on scalp EEGs, in particular at a frequency ≥1.4 Hz. Electrodes showing slow frequency power changes associated with IEDs were consistent with the hemispheric lateralization of IEDs. Electrodes with maximum power of slow activity were not limited to temporal regions but also involved frontal (bilateral or unilateral) regions.

Conclusions: In patients with a clinical picture suggestive of temporal lobe epilepsy, the presence of delta slowing ≥1.4 Hz in anterior temporal regions can represent a scalp marker of hippocampal IEDs. To our best knowledge this is the first study that demonstrates the co-occurrence of ic-IED and increased delta power.

KEYWORDS
delta power, intracranial IED, LRDA, mesial temporal IED, rhythmic delta activity

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INTRODUCTION

The classic interictal epileptiform discharge (IED) or interictal spike consists of a spike or sharp wave followed by a slow wave [1], reflecting a state of hypersynchronous depolarization that is followed by a depression of neuronal activity [2,3].

In patients with focal epilepsy, there is a high spatial correlation between IED and the seizure onset zone. The localization of IEDs provides a very good approximation of the epileptogenic zone [4] and is increasingly validated and used in pre-surgical evaluations of pharmaco-resistant epilepsies [5,6].

Nevertheless, in some cases, IEDs are not detected with scalp electrodes. It has been shown that only 63%–88% of IEDs have scalp electroencephalogram (EEG) correlates visible in routine analysis [7–10]. This is particularly relevant for mesial temporal IEDs that show the lowest detection rate [11,12], especially if compared to IEDs from other regions (e.g. frontal lobe [13]). Magnetoencephalography (MEG) studies suggest similar findings, with a higher detection rate for frontal IEDs compared to medial temporal ones [14,15]. EEGs appear more sensitive than MEG in detecting mesial temporal IEDs [16].

The lack of visibility of mesial temporal IEDs on scalp EEGs has been attributed to a combination of several factors: the specific geometric and anatomical configuration of mesial temporal structures [17,18]; the distance between those structures and scalp electrodes [19]; and the amplitude of background activity that masks IED signals [14]. Further studies have suggested that temporal lobe sources are detectable in scalp EEGs only if interictal or ictal IEDs are not confined to mesial temporal regions but simultaneously involve the lateral part of the temporal lobe [20]. The amplitude [13] of the IED as well as the surface [21,22] of the IED generators play a crucial role in the detection of IEDs on the scalp. IEDs that are not visible on routine visual interpretation can be detected on scalp EEGs after averaging intracranial EEG IEDs, but that implies prior knowledge of when intracranial IEDs (ic-IEDs) occur [13,23]. Nevertheless, to the best of our knowledge, none of these studies looked specifically at how (and if) ic-IEDs, not visible to the scalp as spikes or sharp waves, are represented on the scalp.

Our aim was to evaluate changes in the frequency spectrum on scalp EEGs during intracranial hippocampal IEDs not visible on the scalp, in order to establish if ic-IEDs can be revealed by slow frequencies on the scalp. Simultaneous scalp and ic-EEG recordings were used that provide a unique opportunity to study the interrelations between cortical generators and their scalp correlates.

METHODS

Patients

Simultaneous intracranial high-density EEGs were recorded at the EEG and Epilepsy Unit of the Geneva University Hospital, in 10 patients undergoing invasive pre-surgical evaluation for

FIGURE 1 Intracranial electrode cables (white arrows) and 256 plastic cup scalp electrodes [Colour figure can be viewed at wileyonlinelibrary.com]

pharmaco-resistant epilepsy with stereotactic depth electrodes (SEEG). The study was approved by the ethical committee of the University Hospitals of Geneva.

Electroencephalography acquisition

The simultaneous scalp and intracranial recording was performed on the last day before the removal of the intracranial electrodes. An elastic net of 256 plastic cup scalp electrodes (Electrical Geodesic Inc./Philips Neuro system) was fitted on the patient's head after application of an alcoholic solution on the scalp. All electrodes were filled with a non-sterile conductive paste. A new paste tube was used for each patient to reduce infection risks. The intracranial electrode cables were disconnected prior to the fitting of the scalp net, passed individually through the scalp net and reconnected to the clinical recording system (Figure 1).

Scalp EEG was recorded using the EGI/Philips Neuro Netstation, sampling rate 1000 Hz, and intracranial EEG (ic-EEG) using the System Plus Evolution Micromed, sampling rate 2048 Hz. To ensure time synchronization between the two systems, external triggers were sent by a third computer running E-Prime (Psychology Software Tools), to both acquisition systems. The spatial coverage of intracranial SEEG electrodes is detailed in Table S1.

A board-certified EEG expert (PDS or SV) visually identified and marked epileptic activity (IEDs) on ic-EEG using the usual longitudinal bipolar montage (Table S2). One recording was excluded due to important scalp artefacts and the remaining nine datasets were analysed. Only one type of hippocampal IED for each patient was selected: the most represented and frequent mesial temporal IED, not involving the electrode contacts of the lateral temporal cortex, not visible on the scalp as a spike, or small sharp wave, and occurring in the most prevalent arousal state depending on the individual recording (awake or non-rapid eye movement 1–2). IEDs occurring

simultaneously to electrical or clinical seizures and IEDs of other arousal states than the most prevalent were excluded. Identifiable slow wave was not an exclusion criterion.

As a control condition, ic-EEG epochs without any epileptic activity in the same arousal state as for the selection of IEDs were selected.

One set of intracranial hippocampal IEDs was finally identified for each patient. None of the single IEDs was visible on the scalp. One patient had a parietal opercular dysplasia with very small amplitude IED but also temporally independent hippocampal IEDs and these were selected for analysis. As control, high-density ic-EEGs without any epileptic activity were selected.

For the scalp EEG analysis, our interest was in the correlates of these ic-EEG patterns on a typical clinical EEG recording. Therefore, the high-density EEG set-up was downsampled to a standardized clinical EEG montage with 25 channels (corresponding to the 10–20 international montage plus low temporal electrodes following International Federation of Clinical Neurophysiology recommendations) [24]. Scalp EEG epochs of 2 s around the markers were labelled (i) ic-IED+ and (ii) ic-IED− based on the presence or absence of IEDs visible on intracranial recordings (Figure 2). This selection was performed without considering the presence/absence of visible slow activity on scalp EEGs. Epochs with artefacts related to eye movements or muscle activity were discarded after visual inspection. The selected epochs were exported, downsampled to 200 Hz and filtered in the frequency interval 0.5–30 Hz with a fourth-order Butterworth filter avoiding phase distortion.

Frequency analysis

Single subject level spectral power analysis

In order to get an accurate representation of the spectral power distribution, Welch's power spectral density (PSD) was computed for each 25-scalp electrode. The unit of power was square microvolts per hertz. For each subject, the PSD was averaged in the canonical frequency bands (i.e., delta 0.5–3; theta 4–7; alpha 8–12; low beta 13–17; high beta 18–30) by averaging across all electrodes and for all frequency bins. Our analysis was restricted to frequencies up to 30 Hz due to the lower quality of the EEG above that frequency (50 Hz line noise and other artefacts).

Power values were compared between the two conditions ic-IED+ and ic-IED−. Statistical comparison of the paired-sample t test was computed with the MATLAB '$ttest$' function. The statistical p value was corrected via Bonferroni with a 5*9 factor, that is, the number of frequency bands by number of patients. For each patient the peak frequency in the delta band during periods of ic-IED+ was also reported. For scalp localization, the five electrodes showing strongest power at the peak frequency were reported. When the slowing was ipsilateral in ≥4 electrodes it was defined as 'lateralized' (right or left), whereas if present in at least two electrodes of each hemisphere (two on one side and three on the other side), it was defined as 'bilateral'.

Group level spectral power analysis

At the group level, the previously obtained PSD for each patient was averaged in the canonical frequency bands across patients. As before, the statistical comparison of the paired-sample t test was computed with the MATLAB '$ttest$' function. The statistical p value was corrected via Bonferroni with five factors (i.e., the number of frequency bands). Despite the large difference in IED numbers across patients, only one PSD for each patient and condition was taken for the average.

The power at the frequency peaks in the ic-IED+ and ic-IED− epochs were also statistically compared via t test. Furthermore the effect size was computed for independent variables based on Cohen's d: for $d = 0.01$, very small effect size; for $d = 0.20$, small effect size; for $d = 0.50$, medium effect size; for $d = 0.80$, large effect size; for $d = 1.20$, very large effect size; and for $d = 2.00$, huge effect size.

Data availability statement

The corresponding author has full access to all of the data in the study. He takes full responsibility for the integrity of the data, the accuracy of the data analysis and interpretation, and the conduct of the research. The authors have the right to publish any and all data, separate and apart from the guidance of any sponsor.

RESULTS

Clinical results

The nine patients had a median age of 40 years (range 21–53 years, three female) and median disease onset at 23 years (range 17–39).

The epilepsy was right temporal in three patients, left temporal in two, bi-temporal in three and left parietal in one patient. Hippocampal sclerosis was present in three patients and parietal cortical dysplasia in one patient (but the interictal hippocampal IED was considered temporally independent from the parietal IED, see Methods section), diagnosed by magnetic resonance imaging (MRI) and confirmed histologically. No MRI lesion was found in the remaining five patients, nor at the pathology examination of a surgical sample. Of note, one patient with bi-temporal epilepsy presented hippocampal sclerosis on the right hippocampus and normal hippocampus on the left; one patient considered non-lesional showed the right hippocampus increased in size compared to the left one. The median duration of the simultaneous high-density EEG and SEEG recordings was 32.5 min (range 8.5–41 min). The median number of selected ic-IED+ epochs (and the same number of ic-IED− epochs) was 49 (range 22–204) (Table 1). The number of non-effective medications, interictal positron emission tomography and ictal single-photon emission computed tomography findings of the non-invasive pre-surgical evaluation are detailed in Table S3.
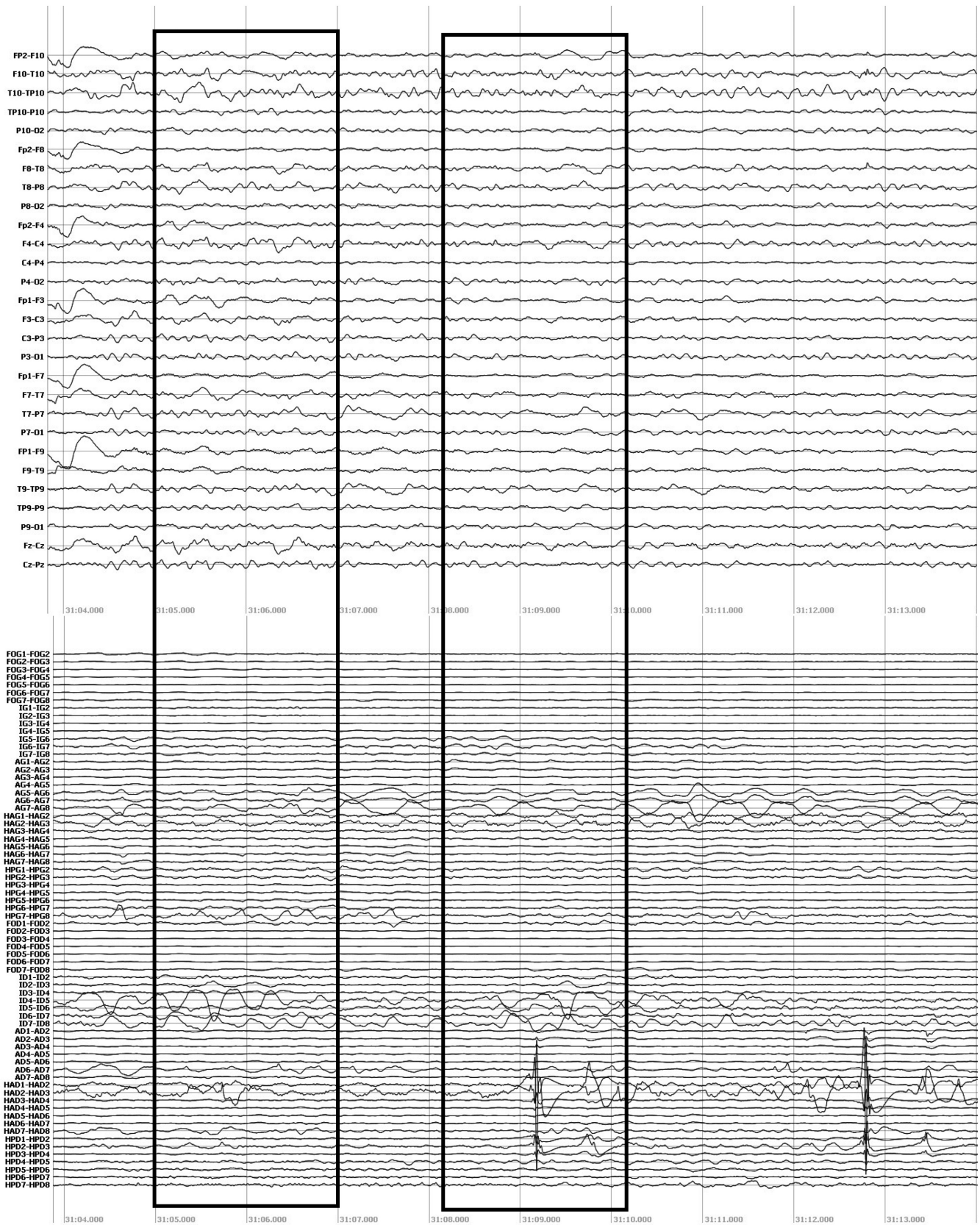
FIGURE 2 Example of 2-s ic-IED− and ic-IED+ epochs. Upper side: 10-s scalp EEG (bipolar montage). Lower side: 10-s intracranial EEG (bipolar montage) showing epileptiform discharges in the right hippocampus. The lateral neocortical contacts of the hippocampal electrode are not affected by the IED (HAD6−8 and HPD6−8)

TABLE 1 Clinical and demographic features of patients

Patient	Age onset epilepsy (years)	Age at recording (years)	Sex	Epilepsy type	MRI/pathology	IED origin taken for analysis	Numbers of epochs	Duration of hd-EEG and SEEG recordings	Arousal state of IEDs
1	14	27	F	L parietal	Cortical dysplasia	L hippocampus	47	29.5 min	Awake
2	36	48	M	R temporal	N	R hippocampus	58	41 min	Awake
3	25	53	F	R temporal	R hippocampus enlargement	R hippocampus	204	35 min	Awake
4	35	38	M	Bilateral temporal	N	R hippocampus	22	8.5 min	Awake
5	17	42	F	L temporal	HS	L hippocampus	137	31 min	Awake
6	17	21	M	Bilateral temporal	N	R hippocampus	97	20 min	Awake
7	39	50	M	Bilateral temporal	R HS	L hippocampus	31	36.5 min	Sleep N2
8	23	27	M	R temporal	N	R hippocampus	49	32.5 min	Awake
9	10	40	M	L temporal	HS	R hippocampus	43	38 min	Awake

Abbreviations: F, female; hd-EEG, high-density electroencephalogram; HS, hippocampal sclerosis; IED, interictal epileptiform discharge; L, left; M, male; MRI, magnetic resonance imaging; N, not-lesional; R, right; SEEG, stereotaxic electroencephalography.

After the invasive pre-surgical evaluation, six patients underwent a surgical resection, and one patient was implanted with thalamic deep brain stimulation (Table S3).

Frequency analysis

Single subject level

At single patient level, all patients showed significantly stronger power in the delta band in the condition ic-IED+ compared to ic-IED−; six patients also showed a stronger power in the theta band during ic-IED+ epochs. Two patients presented stronger power in the alpha band and in one case alpha was stronger in the condition ic-IED− (Figure 3).

During ic-IED+ epochs, the delta slowing was localized either in the frontal temporal regions with lateralization coherent with the origin of the IEDs (5/9) or had a bilateral localization, showing highest power in bilateral frontal temporal regions (4/9). Peak values and channels are shown in Table 2. The median value of the delta peak was 1.5 Hz; the average was 1.6 Hz.

Group level

At the group level, the frequency analysis showed stronger power activity in the delta and theta frequency bands in the ic-IED+ scalp epochs compared to ic-IED− with large effect sizes for delta and theta, medium effect sizes for alpha and low beta and small effect size for high beta (delta, median ic-IED+ 5.90, median ic-IED− 3.06, $p = 0.04$, effect size 0.79; theta, median ic-IED+ 4.38, median ic-IED− 1.40, $p = 0.04$, effect size 0.79; alpha, median ic-IED+ 1.68, median ic-IED− 1.23, $p = 0.16$, effect size 0.51; low beta, median ic-IED+ 0.47, median ic-IED− 0.40, $p = 0.08$, effect size 0.65; high beta, median ic-IED+ 0.18, median ic-IED− 0.15, $p = 0.61$, effect size 0.17) (Figure 4).

The group difference of the power at the ic-IED+ peak frequency was significantly larger in conditions ic-IED+ compared to ic-IED−, with a large effect size (median ic-IED+ 9.13; median ic-IED− 3.46; $p = 0.02$; effect size 0.92) (Figure 5).

DISCUSSION

The aim of our study was to evaluate whether slow frequency power on scalp EEGs increases during intracranial hippocampal IEDs that are not visible on the scalp. The occurrence of ic-IED was demonstrated to be associated with increased delta power on scalp EEG, in particular for frequencies equal to or higher than 1.4 Hz. This could occur even when no slow waves were visually detected on scalp EEG.

Channels showing slow frequency activity showed lateralization consistent with the IED lateralization and revealed a maximum
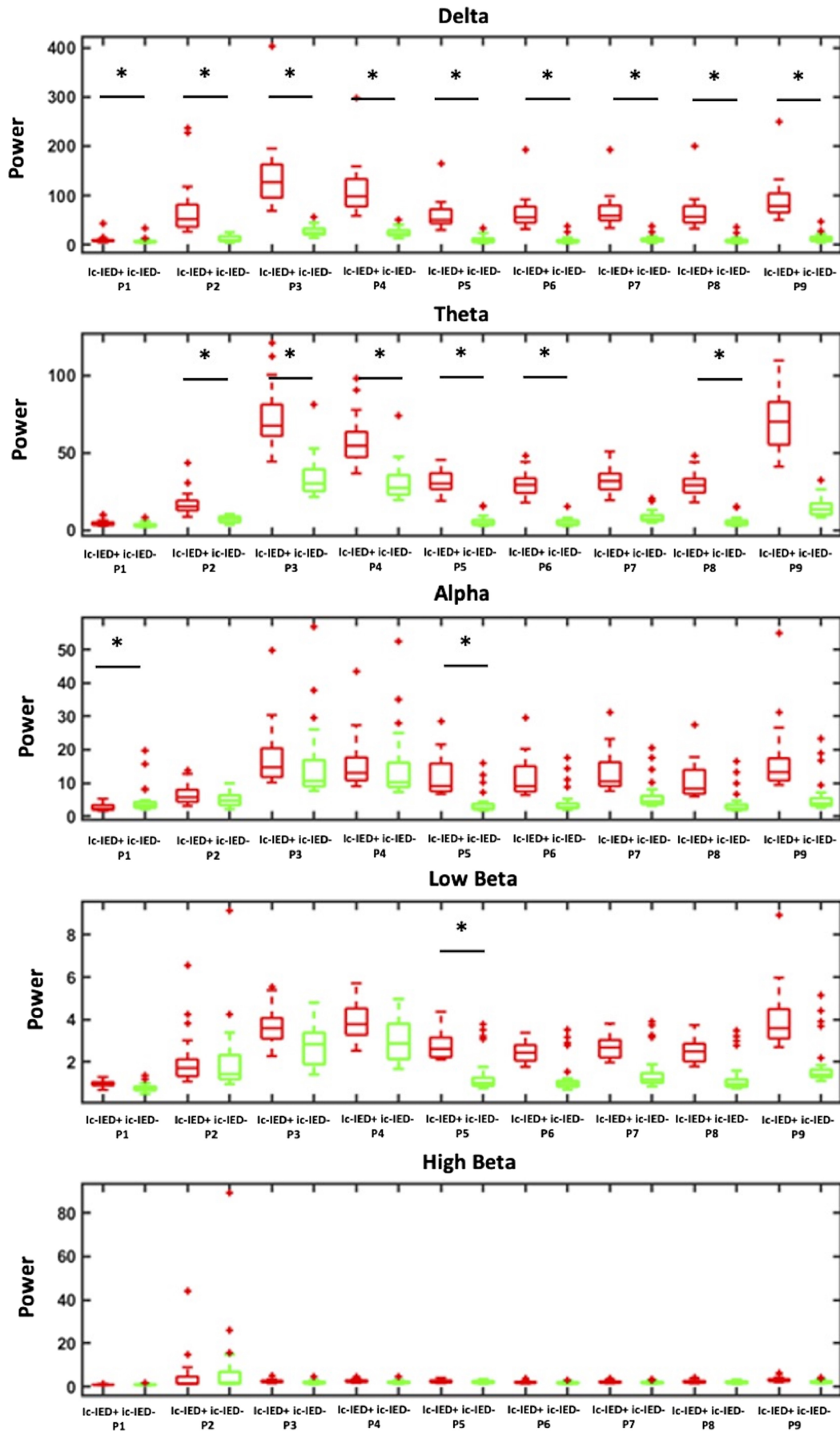
FIGURE 3 Power spectral density for each patient at different frequencies. Box plot of the spectral power in each frequency band. Red, ic-IED+ epochs with cortical IED; green, ic-IED− epochs without cortical IED. Delta 0.5–3; theta 4–7; alpha 8–12; low beta 13–17; high beta 18–30. *$p < 0.01$ (Bonferroni corrected) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Delta peak frequency and localization of delta slowing

Patient	ic-IED	Scalp Frequency peak for ic-IED+ (Hz)	Five channels with maximum power at peak delta frequency	Lateralization of maximal scalp electrode power
1	Hippocampus L	1.6	F7 T9 T7 F9 Cz	L
2	Hippocampus R	1.4	FP2 Fz FP1 F7 T8	Bilateral
3	Hippocampus R	2.6	F8 FP2 FP1 T10 F10	R
4	Hippocampus R	1.9	F8 FP2 FP1 F7 F10	Bilateral
5	Hippocampus L	1.4	FP2 FP1 P9 T10 F10	Bilateral
6	Hippocampus R	1.4	FP2 FP1 T8 T10 F10	R
7	Hippocampus L	1.6	T9 T7 P7 P9 T10	L
8	Hippocampus R	1.2	FP2 FP1 F7 F10 F9	Bilateral
9	Hippocampus R	1.5	F8 FP2 T9 T10 F10	R

Note: Peak frequency in the delta band during periods of ic-IED+ for each patient and the five electrodes showing strongest power at the peak frequency.

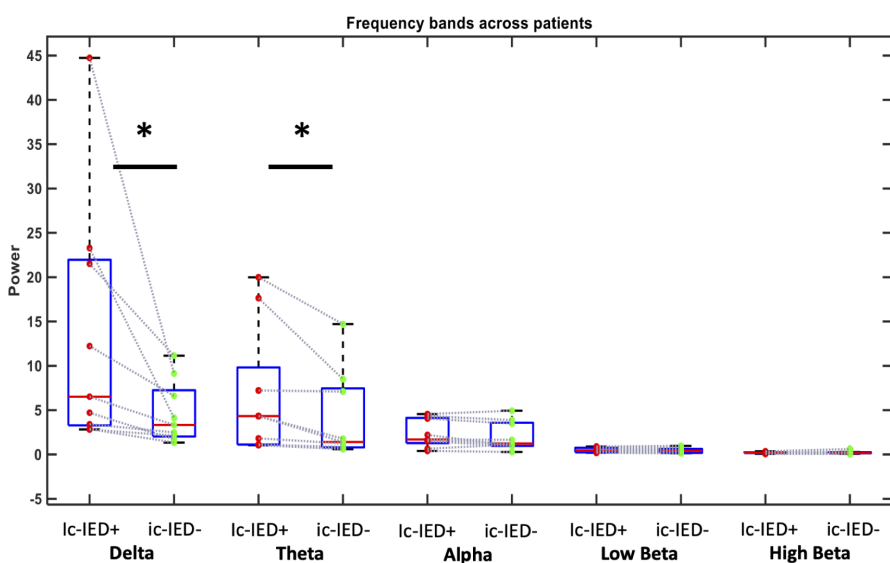Abbreviations: ic-IED, intracranial interictal epileptiform discharge; L, left; R, right.

FIGURE 4 Power spectral density across patients. Box plot of the spectral power in each frequency band for each patient in ic-IED+ (red) and ic-IED− (green). Delta 0.5–3; theta 4–7; alpha 8–12; low beta 13–17; high beta 18–30. *$p < 0.05$ (Bonferroni corrected for five frequency bands) [Colour figure can be viewed at wileyonlinelibrary.com]
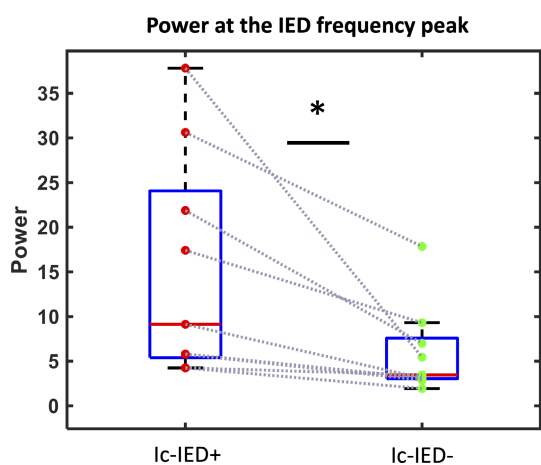

FIGURE 5 Power at the IED frequency peak. Box plot of the power at the peak frequency in the delta band for each patient for epochs with ic-IED+ (red) and ic-IED− (green). *$p < 0.05$ [Colour figure can be viewed at wileyonlinelibrary.com]

activity that was not only limited to temporal regions but involved also anterior (bilateral or unilateral) regions.

Pathological delta activity can present with focal versus generalized/diffuse, and rhythmic or irregular patterns. If diffuse slowing can occur in many clinical pictures (acute/chronic encephalopathies, post-ictal state) as well as in physiological states (sleep, hyperventilation), focal and localized slowing are more correlated with an underlying structural problem [25].

Focal delta slow waves have generally been considered the classic sign of a brain lesion, in particular located at the level of the deep white matter [26–28] or thalamus [29], but studies also demonstrated that they do not have a specific nature and are present in a large range of brain lesions (for instance tumoural lesions [27] or cortical–subcortical abnormalities [30]) and encephalopathic conditions [31].

In the case of frontal delta slowing, often bilateral, with or without a rhythmic feature, the encephalopathic aetiology is the most

frequent [25]. Frontal delta activity was initially considered as originating from subcortical, deep midline structures, although it has subsequently been suggested that this pattern may reflect a pathological hyperactivity occurring in diffuse grey matter disease, at both cortical and subcortical locations [32].

The association of epileptiform activity and seizures with increased low frequency power and slow waves is well established when the delta activity occurs in a rhythmic pattern (rhythmic delta activity [9]). In particular, the risk of seizures is significant in the case of lateralized rhythmic delta activity (LRDA) with a frequency ≥1.5 Hz [33].

This is particularly true for temporal LRDA, where the epileptiform significance is more consistent, being most often associated with anterior temporal spikes (95%) [34]. It is in fact considered an EEG marker of an epileptogenic zone involving the mesial temporal lobe structures [35]. Recently it was shown that intracranial rhythmic hippocampal IEDs were synchronous with 2 Hz LRDA in the frontal temporal region on scalp recording, offering a possible explanation of the epileptiform nature of the rhythmic delta activity [36].

The present study on nine patients goes further in showing how delta activity ≥1.4 Hz can be the scalp representation of a single ic-IED. All but one of our patients presented a peak frequency ≥1.4 Hz. The last patient presented slightly lower peak value (1.2 Hz). The median value of delta peak frequency was 1.5 Hz, and the average was 1.6 Hz. These frequencies are well concordant with the frequency of LRDA typically known to be associated with epileptic seizures. This was found even though LRDA patterns were not present in the EEG selected for analysis (as only isolated IEDs were selected).

The increased delta power detected in our patients was localized in the fronto-temporal regions, unilateral (consistent with the localization of the ic-IED) or bilateral. Depending on the orientation of the temporal cortex affected by IED propagation, the equivalent dipole could be vertical with scalp voltage affected bilaterally in the frontal regions. This could represent a situation in which an underlying epileptic activity cannot be easily distinguished from bilateral bi-anterior slowing related to an encephalopathic mechanism [25].

Considering the hippocampal–neocortical loop, mesial temporal lobe structures receive convergent inputs from a variety of association cortices in the temporal, frontal and parietal lobes and project back to the same structures: the efferent projections from the hippocampus are therefore extremely widespread [37].

When hippocampal IEDs are not visible as IED on scalp recordings, for reasons such as small surface generator [20–22], small IED amplitude [13], configuration [8,19] and distance [19] of mesial temporal structures from the surface, they may still follow temporal–temporal and temporal–frontal projections, losing their hypersynchrony characteristics and generating delta waves from anterior temporal regions.

It cannot be determined if the slow waves represent the aftergoing slow wave of an ic-IED that diffuses to the scalp whilst the IED does not or if it is the IED itself that may influence the electric activity of neighbourhood structures, resulting in slow waves. In the previously published case report, hippocampal IEDs were indeed associated with slow waves in the orbito-frontal regions that were visible on the scalp with similar morphology [36]. Therefore, in patients with a clinical picture suggestive of focal epilepsy, the presence of transient increases of delta slowing ≥1.4 Hz in unilateral or bilateral anterior temporal regions could be suggestive of underlying hippocampal IED.

To the best of our knowledge this is the first study that demonstrates the co-occurrence of an ic-IED and the delta slow activity. The scalp correlates of single IEDs were investigated, and consequently the presence or absence of the rhythmic feature of that slowing, rather attributable to a cluster of IEDs, could not be investigated [36]. Nevertheless, based on our findings it may be assumed that visually detectable, lateralized slow delta activity with rhythmic features (LRDA) would similarly be associated with multiple and rhythmic underlying ic-IEDs.

Limitations

Our study has some limitations. These findings only concern hippocampal IEDs and it cannot be assumed that focal IEDs of other localization (i.e., lateral temporal, frontal, occipital) can similarly be represented on the scalp as higher slow frequency power.

The power values reported in our analysis were not normalized considering the limitation of a small group size and the additional correction for multiple comparisons that it would require. Moreover, the differences in delta power were found with the knowledge of where hippocampal IEDs occurred and there is no immediate way of using these results in clinical practice. Further studies should assess the sensitivity and specificity of the scalp delta power changes in identifying ic-IEDs. Recent studies proposed computational methods allowing scalp signatures of ic-IEDs not visually identifiable on the scalp to be detected [38] or silent mesial temporal lobe seizures from the scalp EEG in Alzheimer's disease to be identified [39].

Further studies are also needed in order to better understand brain regions and networks involved in the generation of slow waves and to confirm our hypothesis that temporal–frontal connections play a crucial role in the origin of delta activity.

Our electrophysiological study is limited to the study of the most prevalent focal IED and did not analyse other IEDs or the localization of the seizure onset or epileptogenic zone. Therefore, it was not possible to correlate our findings with the resection and outcome.

CONFLICT OF INTEREST

AUTHOR CONTRIBUTIONS

Pia De Stefano: Conceptualization (lead); data curation (lead); formal analysis (equal); methodology (equal); validation (equal); visualization (lead); writing—original draft (lead). Margherita Carboni: Data curation (equal); formal analysis (lead); methodology (lead); writing—original draft (equal). Renaud Marquis: Data curation (equal); formal analysis (equal); project administration (equal); software (equal). Laurent Spinelli: Data curation (equal); software (equal); writing—review and editing (equal). Margitta Seeck: Funding acquisition (lead); methodology (supporting); resources (equal); supervision (equal); validation (equal); visualization (supporting); writing—review and editing (equal). Serge Vulliemoz: Conceptualization (lead); data curation (equal); funding acquisition (lead); methodology (equal); project administration (lead); supervision (lead); validation (lead); writing—review and editing (equal).

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