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High-frequency neuronal network modulations encoded in scalp EEG precede the onset of focal seizures

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Abstract

Modulations of neuronal network interactions by seizure precursors are only partially understood and difficult to measure, in part due to inherent intra- and inter-patient seizure heterogeneity and EEG variability. This study investigated preictal neuromodulations associated with seizures originating in the temporal and/or frontal lobes, using information theoretic parameters estimated from awake scalp EEGs in two frequency ranges, 100 Hz and >100 Hz, respectively. Seizure-related activity at high frequencies has not been extensively estimated in awake scalp EEGs. Based on the statistical similarity of preictal and ictal information parameters, preictal network interactions appeared to be specifically modulated at frequencies >100 Hz, but not at lower frequencies. The dynamics of these parameters varied distinctly according to the origin of seizure onset (temporal versus frontal). Although preliminary, and based on a small patient sample for which the potential heterogeneity of multiple anticonvulsive medications was difficult to control, these results suggest that preictal modulations may be estimated from high-frequency scalp EEGs using directional information measures with high specificity to ictal events, and may thus be promising for improving seizure prediction.

Keywords

Epileptic seizures; scalp EEG; preictal dynamics; network interactions; high frequency oscillations; information theory

1. Introduction

Epilepsy is a common, but highly heterogeneous and complex neurological disorder, affecting about 1% of the US population. Seizures evolve dynamically in both time and space, and modulate local and distributed neuronal networks, possibly long before the clinical onset. Therefore, measurable preictal neuromodulations could, in theory, be used for seizure prediction, a problem of significant clinical importance. However, successful prediction requires a clear understanding of the dynamic characteristics of seizure evolution,

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which to date remain only partially understood. Some seizures may be paroxysmal events that occur abruptly and quickly spread to the entire brain, while others evolve gradually and specifically modulate baseline brain activity [35, 28, 29, 32, 33]. In fact, some studies have shown that detectable focal seizure precursors occur minutes if not hours prior to clinical onset [31, 36, 20]. A wide range of quantitative approaches have been proposed for estimating these precursors, with the ultimate goal to design reliable seizure prediction systems. Some of these methods specifically aim to estimate preictal changes in network synchronization, using linear and non-linear measures, including coherence, correlation and phase synchronization indices, similarity indices and measures of non-linear dynamics, e.g., [20, 41, 28, 35], among many others. A few studies have also proposed the combination of multiple methods to improve sensitivity and specificity of seizure prediction [34, 10]. All have advantages and disadvantages, particularly in terms of robustness to the inherently noisy EEG and significant inter- and intra-patient seizure heterogeneity. A detailed discussion of seizure prediction methods is beyond the scope of this study, but an excellent comparison of their characteristics and respective robustness is presented in the critical review by [33]. In general it has proved to be very difficult to consistently estimate seizure-specific, robust precursory neuromodulations from EEG signals.

This study aimed to characterize the preictal dynamics of focal seizures with temporal versus frontal origin, using an information theoretic and thus probabilistic framework for increased robustness. Using this framework, preictal modulations of directional interactions between resting brain networks, possibly associated with seizure precursors, were estimated. A few previous studies have applied information measures to electrophysiological signals in general, e.g., [52, 43], as well as seizure-related EEGs [39]. The latter was one of the first studies to propose information theoretic parameters for quantifying precursory seizure activity and for localizing epileptic foci. In addition, [41] proposed transfer entropy as a measure of directional coordination between EEGs and applied it for epileptic source localization. [30] proposed permutation conditional mutual information as a measure of directional coupling, and [40] estimated ictal modulations of relative entropy in the time-frequency domain. Also, in a small preliminary study, [5] applied permutation entropy to quantify changes in vigilance in the preictal interval. In contrast to previous studies, which have typically estimated parameters at frequencies <80 Hz and in many cases from intracranial EEGs, in this study proposed information measures were estimated exclusively from *awake*, non-invasive (scalp) EEGs, separately at two frequency ranges, 100 Hz and >100 Hz. Epilepsy studies that involve the estimation of information theoretic parameters at frequencies >100 Hz have been very limited, if any. Thus, analysis of scalp-derived network parameters in this range is novel. Due to the inherent noise of the EEG at these frequencies, measures of pairwise network interactions need to be robust to noise. Correlation and coherence measures are sensitive to increased noise levels. Information theoretic, and thus probabilistic parameters may be more robust network measures in the high frequency range. Finally, this study specifically investigated potential differences in preictal neurodynamics of partial focal seizures with temporal or frontal origin, respectively, which may provide important insights into their distinct clinical characteristics.

High-frequency activity (>100 Hz) have been associated with the epileptogenic neural tissue and seizure activity in several studies [22, 51, 25, 16]. Also, significant differences in the correlation between EEGs in the preictal and ictal intervals, in the range 80-200 Hz, have been reported [42]. Experimental models of epilepsy have shown that high-frequency oscillations may occur in association with synchronized epileptic bursts [49, 50, 4, 55]. However, until recently, the majority of human studies at these frequencies were based on intracranial EEGs. An increasing number of studies have demonstrated that high-frequency seizure-related activity is measurable in scalp EEGs [1, 58, 21], during epileptic spasms [26], and more recently in sleep-induced status epilepticus in children [27]. Furthermore, a

recent study showed epileptogenic zone-specific high-frequency activity recorded at the scalp during sleep [1], and further highlighted the need to examine the epileptic scalp EEG at these frequencies. Although the pathophysiology of high-frequency neural activity is not well understood, high-frequency oscillations are thought to reflect short-term changes in network synchronization [3, 12, 23, 13, 11, 24]. There is some controversy regarding the detection and attenuation of high-frequency activity in scalp EEG, due to the presence of the skull and scalp. In many studies, the ratio of the conductivity of the brain to that of the skull is assumed to be $\sim 1:0.0125$ [14]. However, more recent studies have cast some doubt on this ratio, and have proposed a more realistic ratio of $\sim 1:0.065$, resulting in significantly less attenuation of signals propagating through the skull, than previously assumed [38]. In addition, in theory the skull and scalp would not significantly filter out activity in the frequency range 100-250 Hz. Instead, limited propagation and potential coupling of high-frequency oscillations with stochastic activity may, therefore, make them more difficult to identify in scalp EEGs. Nevertheless, this study demonstrated that following appropriate pre-processing, it is possible to estimate cerebral high-frequency activity in *awake* scalp EEG, and that information/entropy measures are appropriate for quantifying neurodynamic network modulations at these frequencies.

2. Methods

2.1. Electrophysiological Data

All scalp EEG data were recorded at Beth Israel Deaconess Medical Center, Boston MA, in the Clinical Neurophysiology Laboratory of the Comprehensive Epilepsy Center. All human studies have been approved by the appropriate ethics committee (the institutional review board) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Subject selection—Seven subjects in the age range 33-91 years ($\mu=47$, ($\sigma=18.8$), were chosen from adult patients who had been admitted to the epilepsy monitoring unit for recording of their typical seizures on scalp EEG. The criteria for inclusion in the study were: 1) 18 years of age or older; 2) diagnosis of focal, medically refractory epilepsy; 3) no prior resective brain surgery; 4) availability of at least two complete seizures, recorded on EEG with adequate technical quality for analysis, and visually identifiable ictal onset and offset according to a reviewing electroencephalographer; 5) availability of at least five periods of non-ictal EEG recordings during wakefulness, at least 30 seconds in duration and partially covering a long period of time (several hours), and occurring more than 12-24 hours remote from a clearly defined ictal event. For one patient, seizures occurred more frequently than once every ~ 12 hours, and thus their baseline EEGs were <12 hours removed from seizure onset. Identified etiologies of epilepsy included hippocampal or mesial temporal atrophy or sclerosis ($n=3$), prior parenchymal brain hemorrhage ($n=1$), gray matter heterotopia ($n=1$), and unknown cause ($n=2$). The localization of seizure onset by cerebral lobe cannot always be definitively determined by visual interpretation of scalp EEG, but the probable seizure foci were located in the temporal lobe ($n=4$), frontal lobe ($n=2$) or both ($n=1$).

Selection of EEG segments—A board-certified clinical neurophysiologist (B.S.C.) reviewed all recordings and excerpted the segments to be analyzed. Ictal onset and offset times, to the nearest half-second, were identified by standard clinical methods of visual EEG interpretation. Specifically, the ictal onset was taken to be the point at which a focal pattern of rhythmic waveforms, representing a distinct change in the background activity and consistent with an ictal evolution (usually with higher-frequency lower-amplitude activity initially, progressing to lower frequencies and higher amplitudes over time), was first seen on the recording. The ictal offset was taken to be the point after which the above-described

rhythmic ictal activity could no longer be seen; activity after this point was often slow and suppressed either focally or in a generalized distribution, suggestive of a postictal state, and did not immediately return to an interictal baseline appearance. A total of 39 preictal intervals, an equal number of ictal EEGs, on average 2 min long, and 42 non-ictal baseline segments were analyzed. EEGs were recorded with a standard international 10-20 EEG system using a referential montage, with channel Cz as the reference channel, and were sampled at 500 Hz. Electrode impedance was in the range 2-5 k Ω , with 5 k Ω being the maximum acceptable impedance, set by the EEG technologists. All seizures occurred during wakefulness, and all baseline segments were also selected from periods of wakefulness. There was no way to determine whether the patients had their eyes open or closed during these intervals. In a previous unrelated EEG study, we have shown that the condition of eyes open/closed does not affect other types of network coordination EEG-based measures in wakefulness, such as relative phase [47]. Preictal intervals were also recorded during wakefulness. The preictal duration varied between patients and seizures, since it was based on the length of available recording prior to clinical onset. Table 1 summarizes the data.

EEG preprocessing—Power-line noise was attenuated with a stopband filterbank of second order elliptical filters centered at the 60 Hz harmonics of the noise, in the range 60-250 Hz, with a 1 Hz bandwidth, 20 dB attenuation in the stopband, and 0.5 dB ripple in the passband. Signals were filtered in both forward and reverse directions to eliminate potential phase distortions due to the non-linear phase of the filter. EEGs were also low-pass filtered with 100 Hz cutoff, for analysis at those frequencies, and high-pass filtered also with the same cutoff, for analysis of high-frequency activity. Artifacts related to eye blinking were eliminated using a matched-filtering approach, where a data-derived blinking waveform was used as the 'stopband' template [45]. Muscle artifacts also often contaminate scalp EEGs, particularly at higher frequencies. Given the specific focus of the study on high-frequency activity, to minimize non-cerebral artifacts in that frequency range, independent component analysis (ICA) was used to decompose the EEG data and eliminate artifact-related components, selected primarily according to their waveforms. Finally, when broadband spikes in the spectrum were suspected to be artifactual, e.g., non-localizable, a median filter was used to suppress them. However, inter-ictal spikes in both baseline and/or preictal segments that were localizable to the region of seizure onset (in cases where this was identifiable), were preserved in the EEG signals, and are considered to be part of a patient's non-ictal baseline. An example of the spectrogram of a filtered and artifact-reduced EEG signal is shown in Figure 1. Two examples of raw and corresponding high-pass filtered EEGs, from two patients are shown in Figure 2. In the top example, a time interval containing sharp waves (50 ms long) is highlighted. The earliest arrivals of these waves were in the left temporal/frontal channels, i.e., in channels covering the region from which seizures were thought to originate from. Measurable delays in their arrivals between channels may be associated with neural propagation. In the bottom example, short ripple complexes (30-50 ms) are highlighted. These waveforms are not identifiable in the raw (unfiltered) EEG (left panel). Their amplitude was on average 10% of the amplitude of the raw signals. In general, measurable EEG amplitude was observed up to 150-180 Hz. High-frequency activity may be localized in time. Thus, in contrast to lower-frequency oscillations which may have approximately constant power during a baseline interval, high-frequency activity may appear intermittently in time, e.g., with burst-like dynamics, and its amplitude may also vary significantly.

Finally, assuming an average total thickness of skull, scalp, and dura of about 20 mm, and an average characteristic propagation velocity of cortico-cortical fibers of 7500 mm/s (typically in the range 6000-9000 mm/s) [37], the presence of the skull and scalp was estimated to be relevant for attenuation/distortion purposes at frequencies >375 Hz, i.e., at lower frequencies, this total thickness is less than the wavelength λ of interest. Evidently,

this is a simplified calculation, and the low conductivity of the skull and distance between the electrical potential generator (the source) and scalp electrodes are likely to be the predominant factors affecting the amplitude of high frequency signals.

2.2. Information Theoretic Measures

The following parameters were estimated, and are described in detail in the Supplemental Information (SI). They were selected for their potential robustness to noise at high frequencies, and their ability to quantify pairwise network interactions and their dependencies. 1) Relative entropy, a non-directional measure of the information one random variable contains about another, which has been used in previous studies to quantify ictal network changes, e.g., [40], 2) conditional mutual information, a directional measure of the reduction in the uncertainty of one random variable due to the knowledge of a second random variable conditioned on a third process, which has been previously applied to quantify pairwise interactions between electrophysiological signals unrelated to EEG and epilepsy, e.g., [52]. Note that the choice of conditioning here is novel. Specifically, spatially averaged EEG cross-correlation, representing a measure of global network coordination in the brain, was used as the conditioning variable. Individual channels may be thought of sampling a spatially large brain network and thus the effects of the connectivity 'state' of this network may need to be accounted for in the estimation of pairwise (local) information/coordination. In general, the conditioning variable is not unique, and may be selected according to the framework of interest. 3) (unconditioned) mutual information, 4) interaction information, the difference between conditional and mutual information, and 5) the directional index of information flow, previously defined differently, in a study unrelated to epilepsy [52], and here computed as the difference between pairwise conditional mutual informations (with alternating conditioning).

Mathematical expressions of all measures and estimation of necessary probability density functions (pdf) are described in the Supplemental Information (S1). EEGs are non-stationary signals, and thus their statistical characteristics may vary dynamically. Thus, prior to pdf estimation, all signals were first segmented according to the criterion of Minimum Description Length (MDL), briefly explained in the Supplemental information, and pdfs/information parameters were estimated for each processing window. The accuracy and robustness of information theoretic measures depends on the estimation of joint and marginal probability distributions. Although there are different ways of estimating these distributions [19], non-parametric, kernel-based methods may be the most reliable, and robust to noise approaches [53][54]. In general, once an appropriate data segmentation method and a reliable estimator of the relevant pdfs have been selected, information measures may potentially quantify network interactions more robustly than other parameters [39]. All statistical calculations in this study assumed a 95% confidence level. Two-sided non-parametric tests, including the Wilcoxon sign-rank (WSR) test, for comparison of means, and the Kolmogorov-Smirnov (KS) statistic, for statistical comparison of probability distributions, were used. Each patient had multiple numbers of baseline, preictal and ictal segments. Thus, statistical differences were assessed for pairwise comparisons (baseline-preictal, baseline-ictal, preictal-ictal), and Bonferroni corrections were made for multiple comparisons. When parameters were averaged over all segments, such corrections were not necessary. Confidence intervals were estimated via bootstrapping. Signal analysis and parameter estimation were performed using the software Matlab (The Math-works Inc). Statistical analysis was performed using the software R.

3. Results

Representative examples from individual patients are shown throughout this section, as well as results averaged over all patient/seizures with the same origin of onset. Segments of

different lengths were aligned at time t_0 and averaged over their common length, unless otherwise noted. When parameters are shown as a function of channels, segments were also averaged over time. In general, the examples shown were selected according to the number of patient seizures and baseline segments, i.e., patients with large number of seizure and multiple baseline intervals, in order to include an adequate range of inter-segment parameter variability. Information parameters were compared between baseline, preictal and ictal intervals.

Relative entropy

Figure 3 shows a representative example of the spatial variation of mean relative entropy for one patient (Patient #6 in Table 1) with seizures originating in the right temporal lobe, at frequencies >100 Hz and 100 Hz, respectively, at baseline, preictal and ictal intervals, as a function of EEG channels. The inter-segment variability is superimposed. Data were averaged over 7 seizures and 9 non-ictal intervals, respectively. At frequencies >100 Hz, baseline and preictal mean relative entropies at each channel were statistically distinct (two-sided WRS test: $p=0.028$, CI: [46.9, 1633.05], two-sided KS test: $p<0.0001$), but preictal and ictal entropies were statistically identical (WRS test: $p=0.152$, CI: [-119.6, 571.6], KS test: $p=0.061$). In contrast, at frequencies 100 Hz, baseline and preictal relative entropies were statistically identical across channels (WRS test: $p=0.31$, CI: [-407, 1158.7], KS test: $p=0.135$), but statistically distinct from ictal entropy (WRS test: $p=0.032$, CI: [37.4, 1017.7], KS-test: $p<0.0001$). Overall, baseline relative entropy across subjects was higher at frequencies >100 Hz, compared to lower frequencies, possibly due to inherent baseline synchronization below 100 Hz in specific networks, such as the default-mode-network [17, 9].

Conditional mutual and interaction information

A representative example of the spatial variation of interaction information, i.e., the difference between conditional and unconditioned mutual information, is shown in Figure 4 as a function of EEG channels, for frequencies >100 (top plots) and 100 Hz, (bottom plots), respectively, and the same patient as in Figure 3. Estimates based on global (black curve), and hemisphere-specific correlations (red, green curves) are superimposed. Parameters were averaged over 7 preictal/ictal segments and 9 baseline epochs, respectively, and over time. Interaction information was always non-negative, i.e., mutual information conditioned on global EEG correlation was always greater than unconditioned mutual information, suggesting a potential effect of global coupling on local network coordination. Differences between global and hemisphere-specific conditioning were insignificant ($p=0.95$, CI: [-110.7, 104.7]). In all patients with temporal lobe seizures, preictal interaction information was significantly lower than baseline and ictal values, at both frequency ranges (WRS test: $p=0.007$, CI: [41.8, 203], KS test: $p<0.0001$), and was also spatially non-specific. In contrast, in patients with frontal seizures, preictal interaction information was significantly higher than baseline, but primarily in bilateral frontal (Fp1, F3, Fp2, F7) and temporal (T3, T4) channels, and significantly lower in central, midline and parietal channels (see Figure 7).

Directionality of information flow

This index was estimated as the difference in conditional mutual information between pairs of EEGs. A positive index $i_{X,Y}$ for channel pair (X , Y) implied that information flow was $X \rightarrow Y$, while a negative $i_{X,Y}$ implied $Y \rightarrow X$. Representative examples for two patients (Patients #6 and #7 in Table 1), with right temporal and right frontal seizures, respectively, are shown in Figures 5 and 6. Indices in Figure 5 are from the same patient as in Figures 1-2. Data were averaged over baseline (9 segments for patient #6, 5 segments for patient #7) and

preictal/ictal-segments (7 segments for patient #6, 6 segments for patient #7), respectively, and over time.

The estimated index varied in the range $[-5, 5]$. To assess random fluctuations in this parameter, 100 Gaussian noise signals were simulated, and $i_{x,y}$ was estimated for each signal pair, and varied in the range $[-0.1, 0.15]$. Thus, a conservative threshold ± 1 was selected, above/below which it was assumed that the index measured true directed information. In both patients and frequency ranges, the directionality of baseline information appeared *spatially* random, i.e., there was no spatial clustering of these values. In patients with temporal lobe seizures, a significant preictal decrease in directional information was observed, particularly above 100 Hz, in agreement with low interaction information in this interval. In contrast, directionally and differentially coordinated regions were observed in the ictal interval at high frequencies, with positive information flow from bilateral frontal/temporal channels to central, parietal and midline channels. In patients with frontal seizures, spatially specific directional interaction between channels was observed, in both preictal and ictal intervals at high frequencies. The directionality index was positive from bilateral frontal, and to a lesser extent from temporal to bilateral central, midline and parietal channels.

Parameters in Figures 3-6 were averaged across time, and thus do not provide dynamic information. However, Figure 7 shows the temporal variation of mean preictal and ictal interaction information at high frequencies. Data were averaged over all temporal-lobe seizures (21 segments, top plots) and frontal seizures (18 segments, bottom plots), respectively. The entire segments were included in the averaging, i.e., not just their common length. All ictal segments were aligned at clinical onset. Mutual information was conditioned on mean global EEG correlation. In seizures of temporal origin, preictal interaction information was on average low (see also Figure 4), until 10-25 s prior to seizure onset. In contrast, ictal interaction information was significantly higher (except in parietal and midline channels), with a short period of significantly lower values at about 75 s from ictal onset. Although this could be an effect of averaging across seizures with slightly different dynamics, it could also reflect a transition to a different dynamic brain state [46] [42]. In seizures with frontal origin, preictal interaction information was spatially specific, i.e., it increased in bilateral frontal and to a lesser extent temporal channels during the entire preictal interval, and in the first ~60s of the ictal epoch. It then decreased monotonically to very low values at seizure offset.

Finally, we examined the dynamics of preictal and ictal network information exchange within the default-mode network (DMN), which has been shown to be active in the resting brain, e.g., [17]. All analyzed segments were recorded at rest. Elements of the DMN include: i) medial prefrontal cortex/left superior frontal gyrus (Brodmann Area (BA) 10, channels Fp1, Fp2, F3, F4), ii) anterior cingulate (BA 24/32 - no scalp electrodes cover the anterior cingulate but we considered channels F3, F4 and Fz as part of that network), iii) lateral parietal cortex (BA 39 - channels P3 and P4), and lateral temporal cortex (BA 21 - channels T3 and T4) [48]. Figure 8 shows mean preictal and ictal directionality index of the DMN. Note that the absolute directionality index was averaged, to avoid misleading nulls resulting from averaging indices with opposite polarity, e.g., $i_{X \rightarrow Y}$ and $i_{Y \rightarrow X}$. As in Figure 5, the entire segments were used in averaging, not just their common length. In patients with seizures of temporal origin, very low preictal directional interactions slowly increased with the approaching clinical onset. The ictal directionality index was significantly higher during the first ~60-70 s of the seizure, decreased to ~0 at about 80 s and again increased in the last 20-30 s of the seizure, similarly to interaction information. In patients with frontal seizures, the directionality index was approximately constant across the preictal interval and

monotonically decreased in the ictal interval to very low values after ~60 s, also consistent with the observed non-directional mutual information.

4. Discussion

Modulations of network interactions by impending seizures originating in temporal and frontal brain regions were investigated at frequencies 100 Hz and >100 Hz, respectively, using both non-directional and directional information theoretic measures. These measures were specifically selected for their potential robustness to noise at high frequencies. Previous studies have used similar measures predominantly for epileptic source localization and network characterization during the ictal interval. However, the application of this framework to quantify transitions in network coordination from baseline to preictal and ictal intervals has been limited [39, 5]. Furthermore, specific investigation of the high-frequency spectrum of the scalp EEG has also been limited, although high-frequency activity has been associated with seizures, the epileptogenic tissue and the ictal interval [22, 16, 1, 26, 27]. Finally, differential neuromodulations due to impending seizures of distinct origin of onset have not been consistently investigated in previous studies.

All estimated preictal parameters varied specifically at high frequencies, but not at frequencies 100 Hz, based on their statistical differences from corresponding baseline values and similarities to ictal values. This indicates that our findings at high-frequencies do not merely reflect some harmonic of a low-frequency change in the preictal EEG, but represent specific high-frequency network modulations. At frequencies 100 Hz, the EEG spectrum is dominated by oscillatory activity which imposes a structure or 'order' on EEG signals. Also, specific resting networks, such as the DMN, are coupled in this frequency range. In contrast, above 100 Hz, fast oscillations and spatially distributed stochastic activity are superimposed in EEGs. Preictal seizure-related neural propagation and aberrant network activation may cause an increase in network 'order' and decrease in distributed (large-scale) random activity, potentially resulting in significant changes in entropy and mutual information.

Preictal modulations of information measures were distinct in the two groups of patients. In patients with temporal lobe seizures, increased, non-directional and spatially non-specific network coordination was estimated. In contrast, in patients with frontal seizures, increased directional coordination, spatially specific to frontal and temporal channels was estimated during the entire preictal interval, with aberrant synchronization probably starting at some earlier time point not included in the analyzed interval. Also, increased preictal interaction information suggested that frontal/temporal network interactions were strongly modulated (enhanced) by the global connectivity of the brain. Preictal asymmetry in mutual information quantified by interaction information has also been reported in a previous study [39].

Ictal network interactions were also distinct in the two patients groups. In patients with temporal lobe seizures, highly directional network interactions, modulated by the global connectivity of the brain, were estimated. A specific temporal pattern was also observed, i.e., two periods of increased directional coupling interrupted by a short period of significantly lower directionality, which may reflect some dynamic 'resetting' mechanism that enables seizure termination. In patients with frontal seizures, highly directional information monotonically decreased during the ictal interval, resulting in non-directional, spatially non-specific coordinated networks in the last ~60 s of these seizures. This pattern may also reflect a different type of mechanism that enables seizure termination.

Although these findings are very promising, the study has some limitations: 1) the results are based on a small number of patients and need to be validated with a larger cohort,

particularly for robust estimation of differences in preictal dynamics of seizures with distinct origin of onset. 2) Being retrospective, the study did not control for patient medications, which may affect neurodynamics and consequently confound the results. Unfortunately, it is difficult to control for the heterogeneity of patient medications in a retrospective study, but despite this limitation, the findings are consistent across patients with seizures originating in the same brain region. Simulations may also be useful to investigate modulations of stochastic activity in noisy, but progressively synchronizing networks, a mechanism that has not been consistently explored, but which is suggested by the findings of this study. In a recent computational study of the hippocampus, [44] have shown that modulations of neuronal (synaptic) noise, in combination with network coupling, give rise to high-frequency oscillations. 3) The preictal interval was defined based on the clinical annotation of the scalp EEG. Ideally, a comparison to the identified ictal onset from intracranial EEG would be necessary to ensure that seizures have not actually started earlier than can be identified on scalp recordings, and that the annotated preictal interval does not include any early ictal activity. Intracranial and/or high-density scalp EEG arrays could also provide further documentation of the occurrence of seizure-related, high-frequency preictal activity. However, none of the patients in this study had intracranial or high-density scalp EEG monitoring performed. 4) There remains the possibility that our methods of EEG recording and pre-processing have not allowed us to properly identify meaningful high-frequency activity of cerebral origin. Thus, analyzed high-frequency could be artifactual, more specifically muscle-related. Furthermore, the presence of the skull, scalp and dura may have differential attenuation effects at distinct frequencies, and may to some extent affect the amplitude of high-frequency activity. Also, the solid angle principle [56] and the findings in [7] suggest that for a potential to be measurable at the scalp, neuronal generators spanning a cortical area of at least 6 cm^2 must be temporally coordinated, so that their individual angles sum up to a sufficiently large solid angle, and consequently potential [15]. Thus, the estimated high frequency activity may originate from relatively large cortical areas, possibly beyond the epileptogenic zone. Although beyond the scope of this study, localization of this activity is important. Despite these limitations, we have applied advanced signal processing approaches for filtering and artifact suppression, and have carefully examined identified waveforms to minimize the possibility of estimated high-frequency activity being artifactual. Also, the robustness and consistency of our findings at low and high frequencies throughout the various peri-ictal time periods, and agreement with existing literature demonstrating that high-frequency seizure-related activity is measurable in scalp EEGs, using techniques and analyses similar to ours, all serve to make this possibility unlikely. Therefore, although this study may be viewed as a preliminary feasibility study, and the results may not lead directly to prediction at this stage, it clearly suggests that information-theoretic measures of network coordination may encode significant preictal and ictal modulations of neuronal interactions by seizure-related activity, in the relatively less explored high-frequency spectrum of the scalp EEG. Furthermore, these parameters may be sensitive to distinct spatio-temporal precursory modulations by impending seizures of distinct focal origin.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- The study investigated preictal modulations of neuronal networks encoded in scalp EEG
- Information theoretic parameters were estimated from baseline, preictal and ictal EEGs
- Seizure precursors modulated these parameters at frequencies >100 Hz but not <100 Hz
- Distinct preictal network interactions were estimated in temporal vs frontal seizures
- Respective ictal network dynamics were also distinct at high frequencies.

Figure 1.

Spectrogram of a single EEG signal (channel T3) following filtering, and artifact suppression via ICA and matched-filtering. Although the highest signal energy is concentrated in the frequency range ~ 1 -35 Hz, there is also significant energy at higher frequencies up to ~ 130 Hz, though more localized at specific time intervals. Note that a decrease in mean spectral power of 6-12 dB, seen at frequencies ~ 80 -130 Hz, corresponds to a decrease in voltage in the range $1/2$ to $1/4$ of the mean signal amplitude in the range 1-35 Hz. Furthermore, the decrease in mean spectral power between ~ 10 and 35 Hz, is ~ 6 -10 dB. Thus, the decrease in mean spectral power from 10-35 Hz is approximately the same as the decrease from 35-130 Hz, indicating measurable EEG amplitude at high frequencies, at least up to 130 Hz in this example. Spectral power decreases by about 20-25 dB at higher frequencies in this particular example.

Figure 2.

Examples of raw (left panels) and high-pass filtered (right panels) EEG signals across channels, from patients #1 (bottom) and #2 (top). In the top example, the highlighted time interval includes sharp wave complexes that are localizable to the seizure onset region (earlier arrival is at channel T5). In the bottom example, the highlighted time interval includes short ripples (30-50 ms), which are consistently detectable in a subset of channels (F7, T3, C3, Fz, Pz, F8, T4, T6, O2), with the earlier arrival in channel T3.

Figure 3.

Spatial distribution of mean relative entropy for one patient (patient #6 in Table 1), at baseline, preictal and ictal intervals, at high frequencies (top plots) and frequencies ≤ 100 Hz (lower plots), as a function of EEG channels. The shaded areas show the variability of this parameter across baseline segments, and preictal/ictal segments. Data have been averaged over all respective seizures/baseline intervals and time, by aligning segments at time t_0 of each interval.

Figure 4.

Mean interaction information for one patient (patient #6 in Table 1), at baseline, preictal and ictal intervals, at frequencies >100 Hz (top plots) and ≤ 100 Hz (bottom plots). Shaded areas show the range of inter-seizure variability of this parameter. The black curve corresponds to mean interaction information with conditioning on mean global signal cross-correlation, whereas the red and green curves correspond to conditioning on mean right and left hemisphere signal correlations, respectively. The scales of the plots at the two frequency ranges are different, but consistent across respective intervals.

Figure 5.

Directionality index, at frequencies >100 Hz (top plots) and frequencies ≤ 100 Hz (bottom plots), at baseline (left), preictal (middle) and ictal intervals (right). The index was averaged over multiple corresponding segments. Data are from one patient with seizures originating in the right temporal lobe (patient #6 in Table 1). Each matrix element represents an estimate of this index. All values across the diagonal are exactly zero as there is no information flow between a signal and itself.

Figure 6. Directionality index, averaged over time and segments, at frequencies >100 Hz (top plots) and frequencies ≤ 100 Hz (bottom plots), at baseline (left), preictal (middle) and ictal intervals (right). The data are from one patient with right frontal seizures (patient #7 in Table 1).

Figure 7. Spatio-temporal variation of preictal and ictal interaction information at frequencies >100 Hz, averaged over all patient and seizures with temporal origin (top plots), and frontal origin (bottom plots), respectively. Mean interaction information at each channel (y-axis) is shown as a function of time (x-axis).

Figure 8.

Preictal and ictal mean absolute index of directionality in the DMN at frequencies >100 Hz, as a function of time, for temporal lobe seizures (top plots), and frontal seizures (bottom plots). These estimates were averaged over all preictal/ictal segments and patients with temporal or frontal seizures, respectively. The shaded areas shown inter-patient variability of the mean indices for each patient.

Table 1

EEG and clinical demographics.

Patient	Focus	# Seizures	Preictal (s)	Ictal (s)	Etiology
1	temporal	9	37-183	55-145	Mesial Sclerosis (L)
2	temporal	3	25-114	76-132	Unknown
3	frontal/temporal	10	45-116	43-125	Unknown
4	frontal	2	143-173	69-120	Mesial Sclerosis (L)
5	temporal	2	131-148	92-119	Periventricular Heterotopia
6	temporal	7	89-157	75-118	Mesial Sclerosis (R)
7	frontal	6	95-108	73-131	Frontal Hematoma (R)