Published in final edited form as:

Epilepsy Res. 2014 December ; 108(10): 1748–1757. doi:10.1016/j.eplesyres.2014.09.002.

AN INTER-ICTAL EEG SPECTRAL METRIC FOR TEMPORAL LOBE EPILEPSY LATERALIZATION

Giridhar P Kalamangalam, MD, DPhil^a, Lukas Cara, BA^a, Nitin Tandon, MD^b, and Jeremy D Slater, MD^a

^aDepartment of Neurology, University of Texas Health Science Center, Houston, TX, USA

^bDepartment of Neurosurgery, University of Texas Health Science Center, Houston, TX, USA

Abstract

Objective—Visually-obvious abnormalities in the resting baseline EEG – slowing, spiking and high-frequency oscillations (HFOs) - are cardinal, though incompletely understood, features of the seizure onset zone in focal epilepsy. We hypothesized that evidence of cortical network dysfunction in temporal lobe epilepsy (TLE) would persist in the absence of visually-classifiable abnormalities in the baseline EEG recorded within the conventional passband, and that metrics of such dysfunction could serve as a lateralizing diagnostic in TLE.

Methods—Epochs of resting EEG without significant abnormalities in light sleep over several days were compared between a group of 10 patients with proven TLE and 10 subjects without epilepsy. A novel laterality metric computed from the line length of normalized power spectra from the temporal channels was compared between the two groups.

Results—Significant group differences in spectral line length laterality metric were found between the TLE and control group. At the individual level, seven of 10 TLE patients had highly significant laterality metrics, all concordant with the known laterality of their disease.

Significance—Detailed spectral analysis offers novel insight into TLE network behavior, independent of the orthodox abnormalities of EEG slowing, spikes or HFOs. The results may be deployed in a practical diagnostic manner, offer insight into the EEG manifestations of disordered cellular network architecture in TLE, and maybe understood through simple analogy with the theory of linear time-invariant physical systems.

Keywords

partial epilepsy; synchronization; epilepsy surgery

© 2014 Elsevier B.V. All rights reserved.

Corresponding author: Dr G P Kalamangalam, Department of Neurology, University of Texas Health Science Center, 7.102 MSB, 6431 Fannin, Houston, TX 77030, USA, Phone: +1 713 500 7117, Fax: +1 713 500 7120, Giridhar.P.Kalamangalam@uth.tmc.edu.

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Abnormalities on the interictal EEG remain of abiding importance in the investigation of suspected partial epilepsy (Selvitelli et al., 2010; Wirrell, 2010). In particular, there is increasing interest in identifying the interictal signatures of seizure-generating brain areas in focal epilepsy (Goldenholz et al., 2012; Medvedev et al., 2011; Megevand et al., 2014; Rodin et al., 2014; Wang et al., 2013). A specific challenge in this context is the development of reliable *noninvasive* EEG markers for the epileptogenic zone. Such markers may eventually eliminate the need for intracranial EEG evaluation and/or the recording of seizures in presurgical epilepsy patients, significantly impacting both the neurobiological understanding and the healthcare economics of refractory epilepsy.

In partial epilepsies as a whole, the presence of a single stable scalp spike focus remains an excellent marker for the epileptogenic zone (Kalamangalam et al., 2009; Megevand et al., 2014). However, in temporal lobe epilepsy (TLE) spikes are often bilateral (So et al., 1989), though methods such as comparison of absolute left-right spike counts may identify the ‘epileptic’ temporal lobe (Krendl et al., 2008). Spike-counting methods however fail in the setting of comparably abundant bilateral spiking, no or rare spikes, multiregional spike populations, or in epilepsies of more heterogeneous origin (Selvitelli et al., 2010). In more recent developments (Goldenholz et al., 2012), high-frequency oscillations (HFOs) detected from scalp EEG may serve as surrogates for the seizure-onset zone. Notwithstanding these advances, there remains a need for newer and effective interictal localization techniques based on scalp EEG in the conventional passband (0.5–70 Hz) employed by the majority of centers worldwide.

In this study, we explored the lateralizing value of a novel metric computed from conventional scalp EEG in 10 patients with proven TLE, contrasted with 10 control subjects without epilepsy. Our work was based on previous ideas (Kalamangalam et al., 2014) regarding electrocorticographic after discharge following cortical electrical stimulation. In that study, we described the after discharge power spectrum having a ‘condensed’ appearance with respect to the baseline (pre-stimulus) spectrum, i.e., having less variance and being more prominently peaked at the maximum. We related condensation to the coalescence of neighboring oscillations (local field potentials) from the breakdown of inhibitory intracortical interactions. In this work, we enlarged our view of epileptiform field potential interactions to include foci of chronic epilepsy. Specifically, we hypothesized that transmission of oscillatory disturbance within or close to areas of focal epilepsy would be less ‘constrained’ than over normal areas – allowing oscillatory instabilities to propagate more readily within the network - and that these changes would be detectable on scalp EEG. We conjectured that altered metrics of oscillatory transmission would persist in the absence of overt spiking or slowing, constituting an independent electrographic lateralizing feature in TLE.

Methods

Data

Ten (six males, four females; age range 22–65 years, median age 42 years) with medically refractory temporal lobe epilepsy who subsequently underwent resective surgery were studied. All patients received comprehensive presurgical evaluation with prolonged video-EEG (VEEG; ‘Phase I’) monitoring in our Epilepsy Monitoring Unit (EMU) for recording of habitual seizures, high resolution cranial MRI at 3T and neuropsychological evaluation. Five patients additionally received metabolic imaging with FDG-PET. In all patients the aggregate of these data suggested a diagnosis of left or right temporal lobe epilepsy, of either mesial or neocortical emphasis. In four patients there was concern about the exact location of the seizure onset zone and its relation to eloquent cortex; these patients underwent subdural grid electrode evaluation (SDE), performed by a single surgeon (NT). In all patients who underwent SDE, ictal onset was localized satisfactorily over the implanted temporal lobe for surgical resection to follow immediately. With one exception, all patients have been followed up post-surgery for more than six months. Nine patients achieved excellent postoperative outcome (Engel IIb or better); in one patient outcome has been less good but nevertheless worthwhile (Engel III).

Clinical details of the TLE patient group are summarized in Table 1.

Phase I interictal EEG data (Nihon-Kohden, Inc., Foothills Ranch, CA, USA; analog data hardware-filtered in the passband 0.5–70 Hz and digitized at 200 Hz,) were reviewed offline in a longitudinal bipolar montage by the first author, a board-certified electroencephalographer. From the continuous multi-day recording eight two-minute epochs of artifact-free EEG in drowsiness or light sleep were chosen for analysis, for a total of 80 epochs. Chosen epochs were judged to be free of obvious persistent abnormalities - spikes, pathological slowing or significant left-right asymmetry. In addition, epochs were from times at least six hours following a prior seizure and at least two hours prior to an ensuing seizure. Selections were made as evenly as possible over the entire patient stay (e.g., data for a patient who stayed five days in the EMU would be collected at 24h intervals as far as possible; data for a patient who stayed two days would be collected 12h apart). A control group of subjects comprised 10 patients admitted to the EMU for VEEG monitoring for investigation of paroxysmal seizure-like spells, in whom epilepsy was eventually excluded and the alternative diagnosis of non-epileptic attacks (psychogenic events) was made. All patients in the control group had normal high-resolution MRI brain scans, a normal neurological examination and no abnormalities on the awake or asleep interictal EEG. Eight two-minute epochs of artifact-free EEG in drowsiness or light sleep were chosen from each control group subject, for a total of 80 epochs. All 160 epochs of patient and control data were subjected to independent review by another author (JDS), also a board-certified electroencephalographer and blinded to subject diagnoses. This author was instructed to score EEG segments as he would in normal clinical practice, grading each EEG as 0 (normal, i.e., no asymmetry), I (questionable asymmetry; clinically insignificant), II (definite asymmetry; clinically significant) or III (florid asymmetry; clinically significant), indicating the abnormal side (left or right).

Analysis

The first five data epochs graded 0 or 1 were analyzed for each subject (see Discussion). Digital EEG data were imported into and processed in MATLAB (The Mathworks, Natick, MA, USA). The temporal derivations of each EEG epoch (channels T3-T5, T5-T7, T4-T6, T6-T8) were isolated and re-referenced to a common average, and analysis was carried out on EEG recorded from the anterior and mid-temporal electrodes (T3-AV/T5-AV and T4-AV/T6-AV, respectively). The power spectrum of each channel was computed by the periodogram method (Karl, 1989), filtered into the 0.5–30 Hz passband, normalized to unit area, smoothed with a 10-point moving average window, vertically scaled to ensure approximate numerical equivalence of the two axes, and visually inspected. Spectra from patients showed a noticeable left-right asymmetry in the fluctuations of the spectral waveform (i.e., line length, that characterized the ‘wiggleness’ of the line about its trajectory) in the canonical δ , θ , and α bands (Figure 2–3), in comparison to normals. Waveform complexity was quantified by computing s , the line length (Guo et al., 2010) of individual spectra over the 2–12 Hz domain; left- and right-sided line lengths (denoted s_L and s_R) were averaged over all data epochs to produce a single left- and a single right-sided line-length metric for each subject (S_L and S_R). Finally, the following index of relative left-right asymmetry was computed:

$$\Delta S = 100 \times \frac{S_L - S_R}{S_L + S_R}.$$

Thus, a subject with a relatively high left-sided spectral line length would have $S_L > S_R$ and index $\Delta S > 0$; similarly a subject with higher right-sided line-length would have $\Delta S < 0$. Subjects without epilepsy (no spectral asymmetry) would be expected to have $\Delta S \approx 0$. Figure 4 is a simple illustration of these calculations in an artificial example. Group differences in the absolute value $|\Delta S|$ between the TLE patient and control patient groups were explored with the independent-samples t test. Significance of each of the TLE patient $|\Delta S|$ values at the individual level was evaluated with a one-sample t test, Bonferroni-corrected for multiple comparisons, with the control group serving as the sample reference population.

The study was approved by the Institutional Review Board of the University of Texas Health Science Center.

Results

Of the 160 EEG epochs initially chosen, 136, 14 and 10 were classified respectively as Grade 0, I or II on blinded review. There were no instances of Grade III abnormalities. Figure 1 shows example EEGs of Grade 0, I and II from different patients.

Figure 2 illustrates the data processing stream for a single EEG epoch from a subject without epilepsy; Figure 3 is a similar illustration for a patient with proven right TLE. These two figures are archetypal of our central result: that line lengths of smoothed spectra were asymmetric in epilepsy patients, in comparison to symmetry in normal subjects. Importantly,

the EEG time-series themselves showed no gross visible asymmetry in either case. In practice, the above calculations were carried out for each data epoch of a subject, and the results averaged to yield the global averages S_L and S_R . Table 2 lists global averaged values, as well as their signed (S) and absolute ($|S|$) differences. Population differences between the two groups (TLE patients and patients without epilepsy) were highly significant (one-way ANOVA, $p < 0.0003$). Statistical testing at the individual level was carried out by performing one sample t tests of each TLE subject's $|S|$ against the normal subject population's mean and variance, using a Bonferroni correction factor of 10. Individual t tests performed in this manner yielded highly significant p -values for seven individuals (patients #1-#5, #8, #10). These data allowed the computation of metrics of the diagnostic accuracy (Kirkwood, 1988) of spectral line length as a diagnostic test in TLE as follows.

$$\begin{aligned}\text{Sensitivity} &= \frac{\text{test positives among TLE subjects}}{\text{all TLE subjects}} = 7/10 = 0.7, \\ \text{specificity} &= \frac{\text{test negatives among normals}}{\text{all normals}} = 10/10 = 1, \text{ and} \\ \text{positive predictive value} &= \frac{\text{test positives among TLE subjects}}{\text{all test positives}} = 7/7 = 1.\end{aligned}$$

Finally, the sign of S in the group of seven TLE patients with significant p values (i.e., the group #1-#5, #8, #10) was concordant with disease laterality in every case ($S > 0$ for right TLE; $S < 0$ for left TLE), implying a lateralization accuracy of 100%.

Discussion

More than 30 years after Rasmussen's evocative classification of interictal EEG spikes as 'red' or 'green' (Rasmussen, 1983), the identification of reliable interictal markers of the epileptogenic zone remains topical. In principle, the dynamic behaviour of a brain area from which seizures arise ought to be identifiably different from that of normal brain, but such clear-cut diagnostic distinction remains elusive. The reasons for failure are possibly two: (i) the notion that TLE, even if 'focal' in the traditional sense, exists along a spatial continuum (Bernasconi et al., 2004), and that sharp demarcations between normal and abnormal areas cannot be found, and (ii) the lack of an appropriate viewpoint from which to make the distinction. Clearly, both reasons could be partly true.

The simplicity of the research question posed in this work mitigated the first of the above issues: we were interested in the determination of laterality only, and all our patients' disease was unambiguously worse on the left or right. Thus, demarcation of abnormal versus normal was unequivocal. We addressed the second issue by considering the EEG as the output of a system of interacting oscillators at multiple time scales (Glass and Mackey, 1987; Kalamangalam et al., 2014; Strogatz, 1994) rather than a time series of voltage changes. Given this 'frequency domain' view, the question of TLE laterality became: how does a system of interacting oscillators capable of sustaining global rhythms of evolving frequency (i.e., a seizure) differ from one that is essentially similar but does not exhibit such behavior? We reasoned that seizure-prone oscillator ensembles sustain rhythms of time-evolving frequency better than normal networks. The resting EEG of seizure-prone brain, if viewed as the frequency response (Lathi, 2000) of a dynamical system, would consequently

possess a more uniform quality to it than the EEG of normal brain; i.e., exhibit a greater homogeneity of scatter of intrinsic frequencies than normal EEG. The latter on the other hand would have more rigid frequency preferences, reflected in an intrinsic frequency profile more tightly organized along the canonical α , β , θ , and δ bands and sub-bands. This difference between epileptic EEG and normal EEG need not depend on total bandwidth; thus, the waveforms could have similar overall frequency content and ‘look’ similar in the time domain, yet have visually obvious changes in the frequency domain. These heuristic expectations were largely confirmed in our work.

Our choice of normal, or nearly normal, EEG from which to make the above distinction was critical to the entire analysis. Clearly, there was little point in identifying metrics of epileptogenicity in EEG already obviously abnormal by visual analysis. Our effort was to identify hidden, but nevertheless robust and systematic, differences in EEG from brain areas prone to seizures versus normal brain areas. Our results nevertheless carry over to the situation when there *is* a significant visual difference between TLE patient and normal subject EEGs. Figure 5 shows a typical example in a patient with left TLE, where the difference in the left and right spectra may be visually understood by the differences in the EEG time series. The right-sided channels have a better developed posterior background rhythm; the left temporal derivations exhibit continuous slowing and scattered higher amplitude slow/sharp transients. As expected, the spectra reflect this difference: power in the alpha band is much higher on the right, and despite the increased slowing on the left, line lengths are still higher overall on the right. However, we anticipate our results becoming inconsistent or breaking down completely in EEGs exhibiting frequent large-amplitude spikes or seizure patterns, due to the qualitatively different neurophysiology that underlies epileptiform paroxysmal change (de Curtis et al., 2012; Kalamangalam et al., 2014).

In the absence of detailed intra and extracellular recording data – as would be obtained in an animal or organotypic model – we may only speculate on the neurophysiological mechanisms underlying our observations. While it is established fact the EEG as recorded from the scalp represents the summed electrotonic potentials across hundreds of cortical macro-columns (Nunez and Srinivasan, 2006; Speckman et al., 2011), the origin of the classical α , β , θ , δ , etc. remains a topic of investigation (Amzica and Lopes da Silva, 2011). Nevertheless, all proposed mechanisms for the structure of the main EEG bands involve specific neuroanatomical structures and their connectivity to each other and the rest of the cortex (Amzica and Lopes da Silva, 2011). Acquired focal epilepsy is uniformly associated with perturbation of normal cortical microstructure by axonal sprouting and recurrent excitation (Dudek and Staley, 2012). Such disordered cellular network architecture naturally yields disorder in EEG rhythm generation (Buzsaki, 2006). Similarly, one may understand why intrinsically aberrant cortical networks, as in focal cortical dysplasia (Thom and Sisodiya, 2008), are associated with a deranged resting EEG profile. On the other hand, the reasons for a uniform spectral profile being better suited to the carriage of epileptic rhythms can be understood via the theory of linear time-invariant (LTI) systems (Lathi, 2000). Assumptions of linearity and time-invariance generally have major limitations; approximation can nevertheless aid intuition and provide insight, and LTI approximations have been used successfully in other models of EEG (Lopes da Silva, 2011). Consider the

‘epileptic’ signal in Figure 6a, synthesized as a time-reversed ‘chirp’ (i.e., a signal whose frequency continuously changes) to reflect one cardinal feature of a seizure: evolution in time. Restricting attention to one signal from one cortical location renders redundant the other main feature of an EEG seizure - evolution in space. Now consider the seizure signal alternately invading normal and epileptic (i.e., close to, or ipsilateral to the seizure onset focus), cortex, with ‘invasion’ modelled as the convolution of the signal with the time course of the resting EEG. It is clear that the normal EEG spectrum, with its bi-humped structure acts somewhat like a comb filter: frequencies between the bands are attenuated, and the signal suffers attenuation when its evolving frequency encounters the gap between the bands. The seizure is poorly sustained and may not propagate. The epileptic EEG spectrum, on the other hand shows less selective attenuation; more frequencies are passed equivalently by its flatter profile, and the signal overall survives the convolution better (Figures 6c1–c2); the seizure is better sustained and may propagate.

We conclude by reiterating the enduring importance of diagnosing the interictal signatures of the seizure onset zone in focal epilepsy. It will be of interest to confirm our observations in an experimental epilepsy setting, as also to study the predictive value of the proposed spectral line-length metric on a prospective basis.

Acknowledgments

We thank our patients for their willingness to allow their EEG data to be used for this analysis, and the technicians and nurses at the Memorial Hermann Hospital Epilepsy Monitoring Unit for their help in the collection of these data. GPK acknowledges a National Institute of Neurological Disorders and Stroke Career Development Award (1K23NS079900-01).

Reference List

- Amzica, F.; Lopes da Silva, FH. Cellular substrates of brain rhythms. In: Schomer, DL.; Lopes da Silva, FH., editors. *Neidermeyer’s electroencephalography*. Lippincott Williams & Wilkins; Philadelphia: 2011. p. 33-64.
- Bernasconi N, Duchesne S, Janke A, Lerch J, Collins DL, Bernasconi A. Whole-brain voxel-based statistical analysis of gray matter and white matter in temporal lobe epilepsy. *Neuroimage*. 2004; 23:717–723. [PubMed: 15488421]
- Buzsaki, G. *Rhythms of the brain*. Oxford University Press; New York: 2006. Structure defines function; p. 29-60.
- de Curtis, M.; Jefferys, JG.; Avoli, M. Interictal epileptiform discharges in partial epilepsy. In: Noebels, JL.; Avoli, M.; Rogawski, MA.; Olsen, RW.; Delgado-Escueta, AV., editors. *Jasper’s basic mechanisms of the epilepsies*. Oxford University Press; New York: 2012. p. 213-227.
- Dudek, FE.; Staley, KJ. The time course and circuit mechanisms of acquired epileptogenesis. In: Noebels, JL.; Avoli, M.; Rogawski, MA.; Olsen, RW.; Delgado-Escueta, AV., editors. *Jasper’s basic mechanisms of the epilepsies*. Oxford University Press; New York: 2012. p. 405-415.
- Glass, L.; Mackey, MC. *From clocks to chaos: The rhythms of life*. Princeton University Press; Princeton: 1987.
- Goldenholz DM, Seyal M, Bateman LM, Gotman J, Andrade-Valenca L, Zelmann R, Dubeau F. Interictal scalp fast oscillations as a marker of the seizure onset zone. *Neurology*. 2012; 78:224–225. [PubMed: 22249499]
- Guo L, Rivero D, Dorado J, Rabunal JR, Pazos A. Automatic epileptic seizure detection in EEGs based on line length feature and artificial neural networks. *J Neurosci Methods*. 2010; 191:101–109. [PubMed: 20595035]

- Kalamangalam GP, Morris HH III, Mani J, Lachhwani DK, Visweswaran S, Bingaman WM. Noninvasive correlates of subdural grid electrographic outcome. *J Clin Neurophysiol.* 2009; 26:333–341. [PubMed: 20168131]
- Kalamangalam GP, Tandon N, Slater JD. Dynamic mechanisms underlying afterdischarge: A human subdural recording study. *Clin Neurophysiol.* 2014; 125:1324–1338. [PubMed: 24365519]
- Karl, JH. Introduction to digital signal processing. Academic Press; London: 1989.
- Kirkwood, BR. Essentials of Medical Statistics. Blackwell Science; Oxford: 1988.
- Krendl R, Lurger S, Baumgartner C. Absolute spike frequency predicts surgical outcome in TLE with unilateral hippocampal atrophy. *Neurology.* 2008; 71:413–418. [PubMed: 18614768]
- Lathi, BP. Signal processing and linear systems. Oxford University Press; New York: 2000.
- Lopes da Silva, FH. Dynamics of EEGs as signals of neuronal populations. In: Schomer, DL.; Lopes da Silva, FH., editors. *Neidermeyer's electroencephalography.* Lippincott Williams & Wilkins; Philadelphia: 2011. p. 65-90.
- Lueders HO, Acharya J, Baumgartner C, Benbadis S, Bleasel A, Burgess R, Dinner DS, Ebner A, Foldvary N, Geller E, Hamer H, Holthausen H, Kotagal P, Morris H, Meencke HJ, Noachtar S, Rosenow F, Sakamoto A, Steinhoff BJ, Tuxhorn I, Wyllie E. Semiological seizure classification. *Epilepsia.* 1998; 39:1006–1013. [PubMed: 9738682]
- Medvedev AV, Murro AM, Meador KJ. Abnormal interictal gamma activity may manifest a seizure onset zone in temporal lobe epilepsy. *Int J Neural Syst.* 2011; 21:103–114. [PubMed: 21442774]
- Megevand P, Spinelli L, Genetti M, Brodbeck V, Momjian S, Schaller K, Michel CM, Vulliemoz S, Seeck M. Electric source imaging of interictal activity accurately localises the seizure onset zone. *J Neurol Neurosurg Psychiatry.* 2014; 85:38–43. [PubMed: 23899624]
- Nunez, PL.; Srinivasan, R. Electric fields of the brain: The neurophysics of EEG. Oxford University Press; New York: 2006. The physics-EEG interface; p. 3-55.
- Rasmussen T. Characteristics of a pure culture of frontal lobe epilepsy. *Epilepsia.* 1983; 24:482–493. [PubMed: 6873005]
- Rodin E, Constantino T, Bigelow J. Interictal infraslow activity in patients with epilepsy. *Clin Neurophysiol.* 2014; 125:919–929. [PubMed: 24239456]
- Selvitelli MF, Walker LM, Schomer DL, Chang BS. The relationship of interictal epileptiform discharges to clinical epilepsy severity: a study of routine electroencephalograms and review of the literature. *J Clin Neurophysiol.* 2010; 27:87–92. [PubMed: 20234317]
- So N, Gloor P, Quesney LF, Jones-Gotman M, Olivier A, Andermann F. Depth electrode investigations in patients with bitemporal epileptiform abnormalities. *Ann Neurol.* 1989; 25:423–431. [PubMed: 2673001]
- Speckman, E-J.; Elger, CE.; Gorji, A. Neurophysiologic basis of EEG and DC potentials. In: Schomer, DL.; Lopes da Silva, FH., editors. *Neidermeyer's electroencephalography.* 6. Lippincott Williams & Wilkins; Philadelphia: 2011. p. 17-31.
- Strogatz, SM. Norbert Wiener's brain waves. In: Levin, SA., editor. *Frontiers in mathematical biology.* Springer-Verlag; Berlin: 1994. p. 122-138.
- Thom, M.; Sisodiya, S. Pathology of neocortical epilepsy. In: Lueders, HO., editor. *Textbook of epilepsy surgery.* Informa UK; London: 2008. p. 1338-1348.
- Wang S, Wang IZ, Bulacio JC, Moshier JC, Gonzalez-Martinez J, Alexopoulos AV, Najm IM, So NK. Ripple classification helps to localize the seizure-onset zone in neocortical epilepsy. *Epilepsia.* 2013; 54:370–376. [PubMed: 23106394]
- Wirrell EC. Prognostic significance of interictal epileptiform discharges in newly diagnosed seizure disorders. *J Clin Neurophysiol.* 2010; 27:239–248. [PubMed: 20634717]

HIGHLIGHTS

- The spectrum of non-diagnostic interictal EEG may be used to lateralize temporal lobe epilepsy;
- The introduced spectral metric performs at 70% sensitivity and 100% specificity;
- The analysis provides novel insight into epilepsy neurophysiology.

Figure 1.

Example 10-second EEG epochs from three patients, illustrating gradations of abnormalities (see text). All tracings shown in a longitudinal bipolar montage, time constant 0.1 s, high-frequency filter 70 Hz, gain 7 $\mu\text{V}/\text{mm}$. a) Grade 0: light sleep in Patient #1 (right TLE with right hippocampal sclerosis). Waveforms are normal and bilaterally symmetric. b) Grade I: Light sleep in Patient #4 (left TLE with left hippocampal sclerosis). The blue circle highlights questionable transient slowing in the left temporal chain. c) Grade II: Quiet wakefulness in Patient #5 (left TLE with left hippocampal sclerosis). The blue circle highlights a significant slow transient. EMG artifact contaminates the frontopolar derivations in this epoch.

Figure 2.

EEG processing stream in a patient without epilepsy (NS# 8). a) 10-s epoch from a longer (2-minute) segment in light sleep, displayed in a longitudinal bipolar montage with time constant 0.1s, low-pass filter set at 70 Hz, and gain 7 $\mu\text{V}/\text{mm}$. The epoch shows no visible asymmetry and was graded 0 by blinded review. b) The four anterior and mid-temporal channels are isolated in an average reference montage for analysis. c) Power spectra comparison. x-axis: frequency in Hz; y-axis power spectral density, individually normalized to unit area and identically scaled to achieve approximate numerical equivalence to the x-axis values. Top panel: The left (blue) and right (red) curves are relatively concordant, indicating a similar distribution of oscillatory power in their respective time-series (T3-AV and T4-AV). Bottom panel: Similar curves for the mid-temporal channels (T5-AV and T6-AV); relative symmetry is again evident.

Figure 3.

EEG processing stream in a right TLE patient (PT #2). a–b) As in Figure 3. Note that this EEG epoch was also graded 0 by blinded review. c) Power spectra comparison. Top and bottom panels: There is visually obvious relative discordance in the profile of the blue and red curves. The red (right) curves appear smoother along their entire domain (0.5–12 Hz). This is particularly evident in the 0.5–4 Hz stretch of the top panel but can also be appreciated in the bottom panel. Smoothness versus ‘bumpiness’ of the waveforms was quantified by line-length (see text and Figure 4), that is larger in this instance for the blue waveforms. That is, $s_R < s_L$.

Figure 4.

Cartoon of line-length and asymmetry index computation in a contrived example. The blue and red curves are normalized and scaled left and right spectral profiles over a 0–10 Hz bandwidth from two representative temporal lobe EEG traces (e.g. T3-AV and T4-AV). Due to normalization, the areas under the curves are equal; their contours are however visibly different. The red curve is smoother and has a less total length (shown by the running arrows) than the blue curve. Thus, $s_L > s_R$, and the ratio $(s_L - s_R)/((s_L + s_R)) > 0$. On the basis of this single EEG epoch, the subject is suspected to have right temporal lobe epilepsy.

Figure 5.

Spectral comparison in the situation of obviously abnormal EEG in a left TLE patient (PT #10). a–b) As in Figure 2. The left-sided temporal derivations exhibit continuous slowing and larger amplitude slow/sharp transients. c) Discordance in spectral profiles. The presence of a well-formed alpha rhythm on the right yields peaks in that frequency on the right; larger slowing on the left is reflected in higher low-frequency amplitudes on the left. Line lengths are overall higher on the right than left.

Figure 6. Chirp signal modelling a seizure, and its processing by normal and epileptic EEG transfer functions. a) Time-reversed epileptic chirp signal with progressively decreasing frequency and increasing amplitude. b1–b2) Spectra of normal (blue, left) and epileptic (red, right) EEGs, exhibiting differing line-lengths but identical area under the curve. c1–c2) The signal suffers visibly greater attenuation on passage through the normal EEG filter than the epileptic EEG filter, due to the former's bilobed character.

Table 1

Demographics, video-EEG monitoring results, imaging findings, neuropsychological deficits, epilepsy syndrome, surgical resection performed and outcome (Engel/ILAE-Weiser) at 6 months. Patient #10 has had only 1 month follow-up so far. Seizure semiologies use the nomenclature of Lueders and coworkers (Lueders et al., 1998): individual seizures comprise one or more phases indexed by a single defining quality, with the ‘→’ symbol indicating continuity.

PT #	AGE/SEX	INTERICTAL EEG	SEIZURE SEMIOLOGY	ICTAL EEG	BRAIN MRI	PET	NEUROPSYCH DEFICIT	EPILEPSY SYNDROME	SURGERY	OUTCOME
1.	65/F	Right > left temporal spikes	Automotor → complex motor	Right temporal, rapid spread to left	Right hippocampal sclerosis	Bilateral temporal hypometabolism, right > left	High average IQ; intact memory	Right mesial temporal	R ATL	1a/1
2.	40/M	Right anterior temporal spikes	Abdominal aura → automotor	Right hemispheric rhythmic delta	Nonlesional	Nonlateralizing	Impaired figural memory	Right mesial	R ATL	1a/1
3.	22/F	Right temporal spikes	Experiential aura → automotor → GTC	Right temporal	Right hippocampal sclerosis	ND	Right frontotemporal dysfunction; poor figural memory	Right mesial temporal	R ATL	1a/1
4.	39/M	Left temporal spikes	Automotor → aphasic → right body clonic	Left temporal	Left hippocampal sclerosis	ND	Left frontotemporal dysfunction; poor verbal memory	Mixed left neocortical\mesial	L ATL	1a/1
5.	52/M	Left temporal spikes	Dialectic→GTC	Left temporal	Left hippocampal sclerosis	ND	Left frontotemporal dysfunction	L mesial temporal	Laser ablation L hippocampus	1a/1
6.	38/M	Right temporal spikes	Automotor → left versive→GTC	Right hemispheric	Right hippocampal sclerosis	Right temporal hypometabolism	Poor figural memory	Right mesial temporal	R ATL	1a/1
7.	30/F	Continuous slow, left temporal; left > right temporal spikes	Unspecified aura → complex motor → generalized tonic-clonic	Left temporal	Nonlesional	L temporal hypometabolism	L frontotemporal dysfunction; intact memory	Left neocortical temporal	L neocortical temporal rxn	3b/4
8.	51/F	Spikes, R & L temporal	Complex partial (dialectic)	L temporal onset; rapid spread to R	L middle fossa encephalocele	L temporal hypometabolism	L frontotemporal dysfunction; intact memory	L neocortical temporal	L neocortical temporal rxn	1b/2
9.	45/M	Left > right temporal spikes	Psychic aura→right versive →GTC	Right temporal	Calcified gliotic lesion L anterobasal temporal	ND	Left frontotemporal dysfunction; intact memory	Left neocortical temporal	L temporal lesionectomy	1a/1 (3 months)
10.	60/M	Spikes, R & L temporal	Complex partial (dialectic) → automotor	L temporal onset; rapid spread to R	L hippocampal sclerosis	Not done	Diffuse cognitive dysfunction	L mesial temporal	L ATL	1a/1

Abbreviations/clarifications: TLE: temporal lobe epilepsy, EEG: scalp electroencephalogram; MRI: magnetic resonance imaging; PET: positron emission tomography. Complex motor: aimless or confused movements of both proximal and distal musculature and/or moderate vocalizations; automotor: chewing or swallowing movements and/or semipurposeful distal hand movements; GTC: generalized tonic-clonic; dialectic: staring and unresponsiveness. L: left; R: R; ATL: anterior temporal lobectomy with amygdala-hippocampectomy; rxn: resection; AMT: anteromesial temporal; NCT: neocortical temporal; ND: not done.

Table 2

‘Wiggliness’ of spectral waveforms in the 2–12 Hz band, quantified by line-length. Individual line lengths of each data epoch were averaged to yield two omnibus values for each subject, S_L (left) and S_R (right). The asymmetry index S quantified the $S_L - S_R$ differences that were generally larger in the patient group compared to normal (one-way ANOVA; $p < 0.0003$). At the individual level, seven patients (#1–#5, #8, #10) had significantly large deviations of $|S|$ from the control population.

	AVERAGE LINE LENGTH (S_L)	AVERAGE LINE LENGTH (S_R)	ASYMMETRY INDEX (S)	EPILEPSY LATERALITY	S	Corrected p -value
PATIENTS						
PT #1	39.80	35.33	5.96	Right	5.96	<0.0001
PT #2	45.94	42.00	4.49	Right	4.49	<0.0001
PT #3	18.99	16.18	7.99	Right	7.99	<0.0001
PT #4	58.64	65.04	-5.17	Left	5.17	<0.0001
PT #5	57.46	67.04	-7.69	Left	7.69	<0.0001
PT #6	37.88	36.64	1.65	Right	1.65	0.91
PT #7	59.16	61.44	-1.89	Left	1.89	0.26
PT #8	52.93	56.72	-3.46	Left	3.46	<0.0001
PT #9	30.56	31.63	-1.71	Left	1.71	0.72
PT #10	74.39	78.57	-2.74	Left	2.74	0.00065

NORMALS					
NS #1	77.35	75.39	1.28	None	1.28
NS #2	31.12	31.20	-0.13	None	0.13
NS #3	36.33	35.46	1.21	None	1.21
NS #4	45.81	47.01	-1.29	None	1.29
NS #5	21.62	21.34	0.64	None	0.64
NS #6	50.34	49.79	0.54	None	0.54
NS #7	58.74	57.23	1.31	None	1.31
NS #8	52.87	53.00	-0.12	None	0.12
NS #9	64.98	63.57	1.1	None	1.10
NS #10	58.79	57.63	0.99	None	0.99