Frequency dependence in the long-range temporal correlation human hippocampus energy fluctuations

M. Stead[1], G.A. Worrell[1], and B. Litt[2]

[1]Department of Neurology

Mayo Clinic

Rochester, Minnesota, 55905

[2]Department of Neurology

Hospital of the University of Pennsylvania

Philadelphia, Pennsylvania, 19104

Correspondence should be addressed to:

G.A. Worrell (Worrell.Gregory@mayo.edu)

Mayo Clinic

200 First Street SW

Rochester, MN 55905

Telephone: 507-284-1588

Fax: 507-284-4795

Abbreviations

DFA: Detrended fluctuation analysis

EEG: Electroencephalogram

LRTC: Long-range temporal correlations

CWT: Continuous wavelet transform

r.m.s: Root-mean-square

Keywords: EEG, Long-range correlations, Hippocampus, Epilepsy, and Scaling Behavior.

ABSTRACT

Spontaneous energy fluctuations in human hippocampal EEG show prominent amplitude and temporal variability. Here we show hippocampal energy fluctuations *often* exhibit long-range temporal correlations with power-law scaling. During these epochs we find that the energy fluctuations exhibit LRTC over a broad frequency range (0.5- 100 Hz) with greater persistence of the correlations in the 0.5-30 Hz range compared to 30-100 Hz. The correlation in hippocampal energy fluctuations is characterized by a bias for energy fluctuations to be followed by similar magnitude fluctuations over all energy scales, i.e. large begets large and small begets small.

INTRODUCTION:

The origin and functional correlates of hippocampal EEG oscillations remain active areas of research [2, 6, 8, 10]. Hippocampal EEG activity, as measured by depth electrode recordings, is generated by local populations of synchronously firing neurons and when examined over sufficiently long time scales (~ minutes) exhibits a wide range of amplitude and temporal variation that have received little attention [17]. Unfortunately, most quantitative methods for studying the temporal dynamics of the EEG, such as spectral analysis and nonlinear dynamics [12, 15] require stationary EEG. While the energy of human hippocampal EEG may remain nearly constant for minutes at a time the mean energy and variance can also fluctuates widely [3], limiting the usefulness of standard spectral and non-linear dynamics methods for investigating correlations over long time scales. For this reason, complete characterization of the long-range temporal correlations (LRTC) in EEG fluctuations, and in turn the collective neuronal oscillations responsible for the EEG, have received little attention.

In recent years, new methods have been developed which make the problem of analyzing LRTC in non-stationary data tractable. Detrended fluctuation analysis (DFA) is one such method [1, 7, 13]. It provides a systematic method for the analysis and characterization of LRTC embedded in non-stationary time series. Detrending the signal on multiple time scales to eliminate spurious detection of temporal correlations that arise as an artifact of signal non-stationarity allows the determination of intrinsic scaling exponents that characterize temporal correlations in mono-fractal signals [11]. Recently, DFA has been used to demonstrate the presence of LRTC with power-law scaling in human EEG recorded from the scalp [5, 9].

Here we use DFA to analyze energy fluctuations in long continuous EEG time series obtained from intracranial hippocampal depth electrodes placed in five consecutive patients with unilateral mesial (amygdalohippocampal) temporal lobe epilepsy undergoing pre-surgical evaluation.

METHODS

EEG recording:

Intracranial EEG was obtained from chronically implanted depth electrodes in the long axis of the hippocampus of both temporal lobes in five adult epileptic patients being evaluated for epilepsy surgery. The data were recorded using a referential montage and then low-pass analog filtered at 100 Hz and digitized at 200 Hz.

Five randomly selected 20-minute EEG segments were selected for each patient in each of three states: awake, asleep, and preseizure awake, yielding a total of fifteen 20-minute segments of intracranial EEG for each of the five patients. Seizure onset lead and time were determined by visual inspection by an epileptologist (GAW or BL). A second lead was identified, herein referred to as the remote lead, which was in the contralateral hippocampus and electrographically removed from the seizure onset zone.

Determination of behavioral state:

Continuous video of the patient's entire monitoring stay were viewed in to determine the patient's behavioral state (sleep/wake) and identify clinical seizures. Behavior clearly recognized

as wake or sleep were recorded, and then the intracranial EEG was quantitatively analyzed to achieve finer resolution of sleep-wake cycles into slow-wave sleep, wakefulness, and indeterminate periods.

Wavelet Filtering:

The data were analyzed in four forms: unfiltered (other than by the low-pass analog filter), low-frequency (0.5 to 30 Hz), high-frequency (30 to 100 Hz), and the standard clinical EEG bands, delta(0.5-4 Hz), theta(4-8 Hz), alpha(8-12 Hz), beta(12-30), and gamma(30-50 Hz). The off-line filtering was performed with a wavelet filtering scheme. Wavelet filtering was selected due to its robust detection of temporally limited frequencies common in EEG tracings.

To facilitate arbitrary frequency band selection the continuous wavelet transform (CWT) was used despite its significant computational burden relative to the discrete transform. The CWT, W, of a one-dimensional signal, $f(x)$, is defined as $W(a,b) = \frac{1}{\sqrt{a}}\int_{-\infty}^{+\infty} f(x)\psi^*\left(\frac{x-b}{a}\right)dx$ where a represents the wavelet scale, b the wavelet center offset, and $\psi^*(x)$ the complex conjugate of the wavelet function. The "gaus4" wavelet, the normalized 4th derivative of a gaussian, was used because of its compatibility with the CWT, the absence of an imaginary component for computational efficiency, and its relative simplicity.

Energy Calculation:

The filtered and unfiltered tracings were transformed to instantaneous energy. Imposing a fixed window for averaging the voltages or their squares imposes arbitrary limits on resolution of the

fluctuations in the new signal (Figure 1.). Notably, simply determining the energy from the square of the voltage also produces a self-similar energy time series [17].

Long-range temporal correlations and Detrended Fluctuation Analysis:

This method has been well described in other papers [1, 7, 13], and will be discussed only briefly. Detrended fluctuation analysis (DFA) is a scaling analysis method that can be used to detect LRTC in noisy non-stationary signals. The fundamental idea is to determine how the average root-mean-square (r.m.s) fluctuation, $F[\tau_l]$, of the integrated time series of interest varies as a function of the time scale. Using DFA to calculate the average r.m.s fluctuations it can be shown that when LRTC are present $F[\tau_l] \propto \tau_l^{H}$, where H is the exponent that characterizes the power-law decay of the temporal correlations in the time series of interest [13]. The exponent H is often called the Hurst exponent [11].

To determine the scaling constant H the root-mean-square fluctuation of the detrended time series

$$F[\tau_l] = \frac{1}{m}\sum_{j=1}^{m}\sqrt{\frac{1}{l}\sum_{k=1}^{l}\left(Y[k] - Y_l[k]\right)^2} \qquad (3)$$

is calculated for a range of window sizes τ_l. The "integrated displacement" of the time series is $Y[k] = \sum_{i=1}^{k}\left(E[i]\right)$, where $E[i]$ is the energy at discrete time i. The entire time series of length N is divided into $m = N/l$ nonoverlapping windows (overlapping windows could be used as well) each of length l, and in each window the "local trend $Y_l[k]$" is calculated. Signals with LRTC

and power-law scaling yield a linear relation on a log-log plot, i.e. $\log(F[\tau_l]) \propto H \log \tau_l$, and the scaling exponent H can be obtained by linear regression analysis (Fig. 2).

DFA method was verified using simulated time series with specific LRTC characteristics, i.e. particular values of H [11, 14] (Figure 3). The artificial data were stationary allowing spectral methods to be used as a reference. Ten thousand novel data sets of 10^6 points each were generated for each scaling constant. The DFA was calculated for each set, and the standard deviation of the scaling constants from the collection of the 10^4 sets.

Most of the DFA curves had two distinct linear regions, one at short time scales with exponents outside the range seen with LRTC scaling and a second at longer time scales with LRTC. We developed a systematic method to fit the two regions. The derivative of the DFA curve was generated, and three lines were fit to the derivative with two of zero slope at either ends of the DFA curve, connected by a segment of arbitrary slope (Figure 2). The set of three lines which best fit the data determined the cut points for fitting the two lines to the original DFA points.

RESULTS:

The intracranial EEG displayed simple power law scaling by DFA analysis in 429 of the 450 data sets analyzed. Twenty-one data sets were excluded from statistical analysis because their DFA plots appeared to contain more than two linear regions (figure 2, right). Every DFA plot contained at least 2 linear regions, the first region being an artifact of the dominant frequency in the tracing after filtering [11]. The scaling constants in this region were uniformly greater than

one, beyond the range defined for LRTCs. The scaling constants of the second linear segment of the DFA curve all fell between 0.5 and 1.0, the range defining LRTC and power-law scaling behavior.

Five 20-minute segments of EEG were analyzed for each condition. The variables were patient, behavioral state, frequency band, and recording lead. The five scaling constants for each condition were averaged, and these averages compared using paired two-tailed t-tests.

Scaling constant means paired for patient and behavioral state were compared between the low and high-frequency bands defined as 0.5-30, and 30-100 Hz respectively. The low-frequency filtered data showed significantly larger scaling constants than the higher frequency bands in both the seizure onset and remote leads ($p = 1.3 \times 10^{-9}$ onset, $p = 3.6 \times 10^{-5}$ remote, figure 4). A similar comparison was made on the more narrowly defined clinical EEG bands, δ, θ, α, β, and γ, but no statistically significant difference was detected in the scaling constants in this analysis.

Comparison of the scaling constants across the behavioral states awake and asleep did not demonstrate an overall statistically significant difference. However when further separated by the frequency band a difference was detected, with the low frequency band in the awake state demonstrating significantly larger scaling constants ($p = 0.034$ onset, $p = 0.22$ remote). Comparisons between the awake and awake-preseizure tracings did not reveal any significant differences in the scaling constants. Nor were there significant differences in the scaling constants between the seizure-onset and seizure-remote leads.

DISCUSSION

We have demonstrated that for long epochs (minutes) the energy fluctuations in human hippocampal EEG exhibit power-law scaling and LRTC. The scaling exponent provides a quantitative measure of the temporal correlations that exist in the energy time series. When the signal is completely uncorrelated (Gaussian or non-Gaussian probability distributions), the calculation of the scaling exponent yields $H = 0.5$. This is easily demonstrated by randomly shuffling the energy time series. When applied to a signal with LRTC and power-law scaling DFA will generate scaling exponents with either $0 < H < 0.5$ or $0.5 < H < 1$. When $0.5 < \alpha \leq 1$, as seen in here in human hippocampal EEG, the data is correlated such that large(small) energy fluctuations are likely to be followed by large(small) energy fluctuations. When $H = 1$ the LRTC become independent of time with infinite range, and as H increases from $H \geq 0.5$ toward $H = 1$, the temporal correlations in the time series are more persistent (decay more slowly with time). When $H > 1$, however, the correlations no longer exhibit power-law scaling and decay more rapidly .

The physiologic mechanism(s) responsible for LRTC of hippocampal energy fluctuations energy fluctuations are not known, but simulations demonstrate [4] that the introduction of a biased probability distributions can produce LRTC with scaling exponents $0.5<\alpha<1.0$. While LRTC in the temporal dynamics do not implicate a unique mechanism, recent studies show that aggregate time series made up of elements with heavy tailed distributions exhibit similar behavior [16].

Acknowledgments: This work was supported by the National Institutes of Health Grants # K23 NS047495-01 (GAW), RO1NS041811-01 and MH-62298RO1 (BL).

REFERENCES

1. Buldyrev, S.V., A.L. Goldberger, S. Havlin, R.N. Mantegna, M.E. Matsa, C.K. Peng, M. Simons, and H.E. Stanley, *Long-range correlation properties of coding and noncoding DNA sequences: GenBank analysis.* Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics, 1995. **51**(5): p. 5084-91.
2. Buzsaki, G., *Theta Oscillations in the hippocampus.* Neuron, 2002. **33**(3): p. 325-40.
3. Cranstoun, S.D., H.C. Ombao, R. von Sachs, W. Guo, and B. Litt, *Time-Frequency Spectral Estimation of Multichannel EEG using the Auto-SLEX Method.* IEEE Transactions on Bioengineering, 2002. **49**(9): p. 988-996.
4. Feder, J., *Fractals*. 1988, New York: Plenum.
5. Ferree, T. and R. Hwa, *Power-law scaling in human EEG: Relation to Fourier power spectrum.* Neurocomputing, 2003. **52**: p. 755-761.
6. Howard, M., D. Rizzuto, J. Caplan, J. Madsen, J. Lisman, R. Aschenbrenner-Scheibe, A. Schulze-Bonhage, and M. Kahana, *Gamma oscillations correlate with working memory load in humans.* Cerebral Cortex, 2003. **13**(12): p. 1369-74.
7. Ivanov, P., A. Bunde, L.A. Amaral, S. Havlin, J. Fritsch-Yelle, R.M. Baevsky, H.E. Stanley, and A.L. Goldberger, *Sleep-wake differences in scaling behavior of the human heartbeat: analysis of terrestrial and long-term space flight data.* Europhys Lett, 1999. **48**(5): p. 594-600.

8. Kahana, M., R. Sekuler, J. Caplan, M. Kirschen, and J. Madsn, *Human theta oscillations exhibit task dependence during virtual maze.* Journal Neuroscience, 1999. **399**: p. 781-784.

9. Linkenkaer-Hansen, K., V.V. Nikouline, J.M. Palva, and R.J. Ilmoniemi, *Long-range temporal correlations and scaling behavior in human brain oscillations.* J Neurosci, 2001. **21**(4): p. 1370-7.

10. Lisman, J. and M. Idiart, *Storage of 7 ± 2 short-term memories in oscillatory subcycles.* Science, 1995. **267**: p. 1512-1515.

11. Mandelbrot, B., *Gaussian Self-Affinity and Fractals*. 2002, Berlin: Springer-Verlag.

12. Palus, M., *Nonlinearity in normal human EEG: cycles, temporal asymmetry, nonstationarity and randomness, not chaos.* Biol Cybern, 1996. **75**(5): p. 389-96.

13. Peng, C.K., S. Havlin, H.E. Stanley, and A.L. Goldberger, *Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series.* Chaos, 1995. **5**(1): p. 82-7.

14. Rangarajan, G. and M. Ding, *Integrated approach to the assessment of long range correlation in time series data.* Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics, 2000. **61(2)**: p. 4991-5001.

15. Stam, C.J., J.P. Pijn, P. Suffczynski, and F.H. Lopes da Silva, *Dynamics of the human alpha rhythm: evidence for non-linearity?* Clin Neurophysiol, 1999. **110**(10): p. 1801-13.

16. Willinger, W., M. Taqqu, R. Sherman, and D. Wison, *Self-similarity through high-variability: statistical analysis of Ethernets LAN traffic at the source level.* IEEE/ACM Trans. Networking, 1997. **5**: p. 1-15.

17. Worrell, G., S.D. Cranstoun, J. Echauz, and B. Litt, *Evidence for SOC in human epileptic hippocampus.* NeuroReport, 2002. **13(16)**.

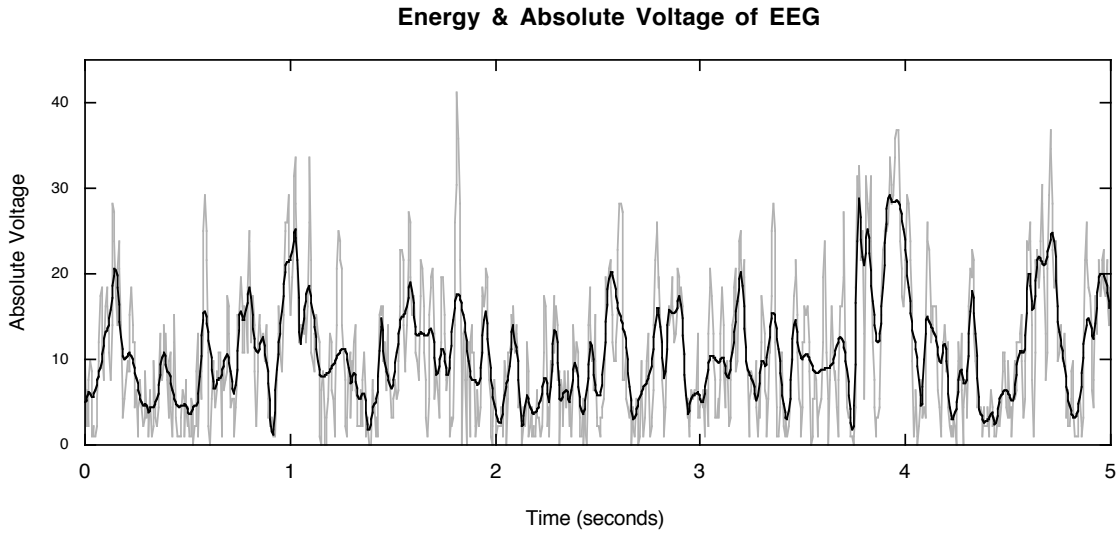


Figure 1: Plot of the absolute value of the EEG voltage (gray) and the energy function (black). The energy function was generated by integrating the data between successive peaks, and separately between successive troughs. The integral values were normalized by the length of their respective waveforms and aligned to the original time sequence at the waveform midpoints form a series of anchors. Values between the successive anchor points were generated by cubic spline interpolation.

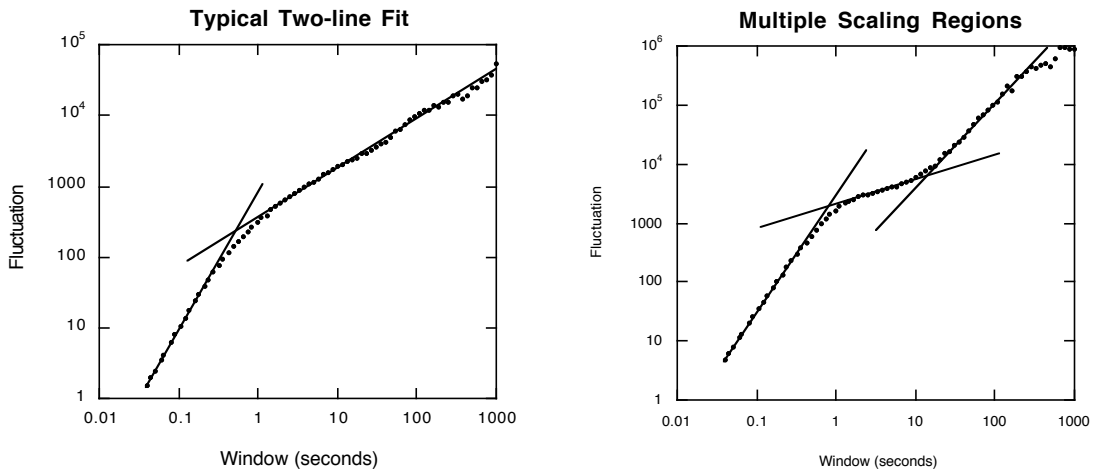


Figure 2: Most of our data were fit with two lines similar to the plot on the left. The lines were chosen by fitting an estimate of the derivative of the DFA function by three line segments: two with zero slope, connected by one of arbitrary slope. The combination of lines that minimized the total deviation was used to select the boundaries for fitting the two lines in the original data. A weighted least squares was used for the final fits. The weighting function was the square root of the number of data windows used to generate each point. Twenty-one of our 450 DFAs were clearly not well represented by a two line fit. These were censored from further analysis. One of these plots, with putative fitting lines is displayed in the right of the figure.

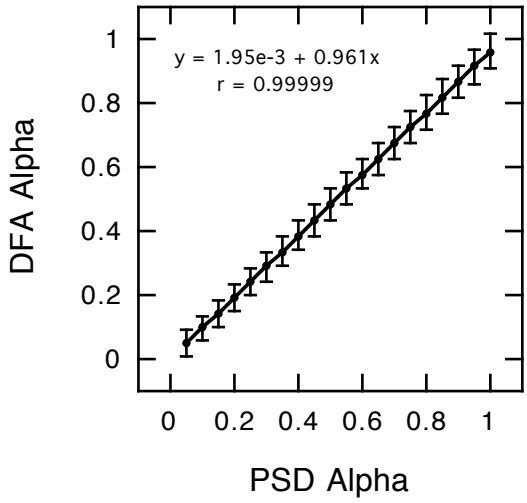
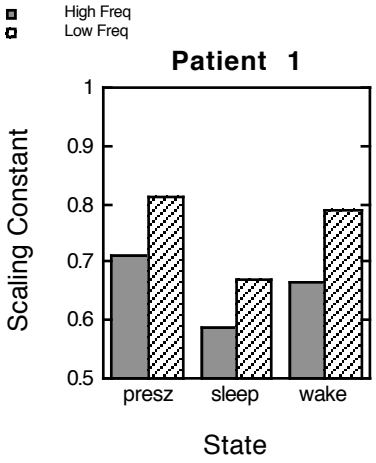
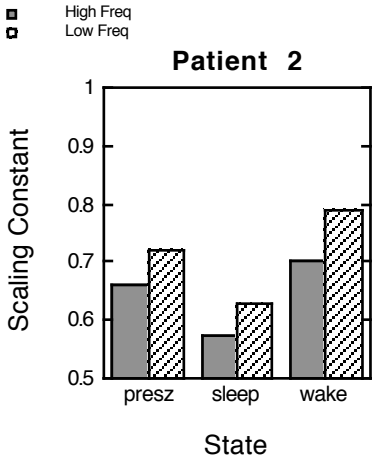
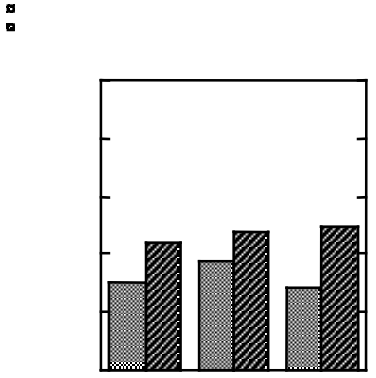


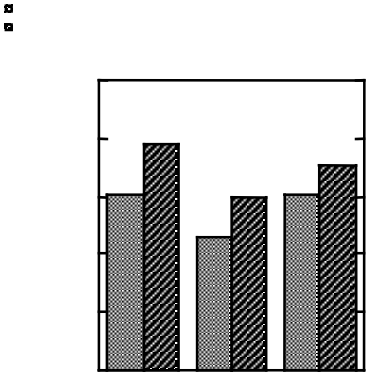
Figure 3: Results of a Monte Carlo simulation using our DFA algorithm. Each point is the mean of the scaling constants derived from 10^4 randomly generated stationary data sets with predesignated scaling constants, each set containing 10^6 points. The scaling constant was derived from the power spectrum (PSD) and DFA for each set. The error bars represent two standard deviations of the DFA scaling constants at each point. One standard deviation was approximately 0.02 at all the points.



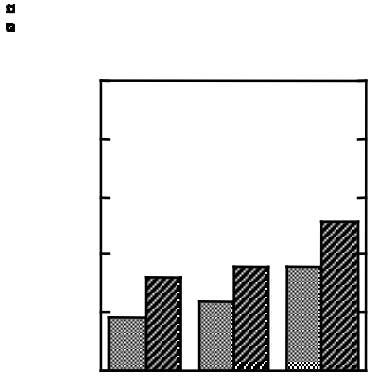


0.50.60.70.80.91preszsleepwake**Patient 3**High FreqLo0.50.60.70.80.91preszsleepwake**Patient 4**High FreqLo





0.50.60.70.80.91preszsleepwake**Patient 5**High FreqLo



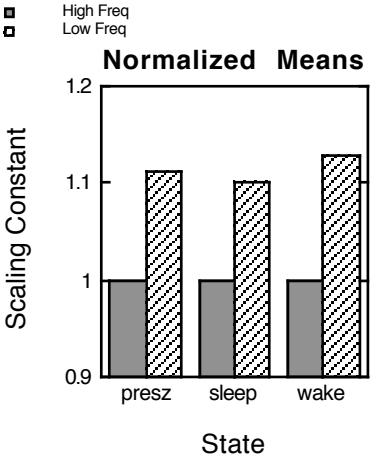


Figure 4: The long range temporal correlations from each patient in each state were less persistent in the high frequency range (30-100 Hz) than the low range (0.5-30 Hz). Long range temporal correlations are present in all conditions. The above data are generated from the seizure onset electrode but are not qualitatively or statistically different in the remote lead. The lower right graph is generated by normalizing each low frequency scaling constant by its high frequency counterpart and averaging across patients, to demonstrate the relative average difference in magnitude of the scaling constants across all the patients.

Gregory Worrell

Matt Stead

Brian Litt

Brian Litt received the A.B. degree in engineering and applied science from Harvard University in 1982 and the M.D. degree from Johns Hopkins University in 1986. Residency in Neurology, Johns Hopkins University, 1988–1991. Neurology Faculty, Johns Hopkins Hospital, 1991–1996. Neurology/Biomedical Engineering Faculty, Emory University/Georgia Institute of Technology 1997–1999. Dr. Litt is an Assistant

Professor of Neurology; Assistant Professor of Bioengineering, Director, EEG Laboratory and Epilepsy Surgery Program University of Pennsylvania