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A unified statistical model for the human electrocorticogram

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Abstract

Objective—Extracellular field potentials (ECFs) generated in the cerebral cortex span a vast range of spatiotemporal scales. The process(es) leading to this large dynamic range remain debatable. Here we propose a novel statistical description of the amplitude spectrum of the human electrocorticogram (ECoG).

Methods—Spectral analysis was performed on long-term recordings from epilepsy patients undergoing pre-surgical evaluation with intracranial electrodes. Amplitude spectra were fit with a multi-component Gaussian model on semi-logarithmic axes.

Results—The Gaussian formulation provided excellent fits to the data. It also suggested how the changes accompanying the sleep-wake cycle and certain epileptiform transitions could be understood by variation in the parameters of the model.

Conclusions—The proposed continuum model synthesizes several previous observations regarding the statistical structure of the resting human ECoG. It offers a conceptual platform for understanding the EEG changes accompanying the sleep-wake cycle and pathologically hypersynchronous behavior.

Significance—Statistical characterization of the spectral distribution of field potentials yield insight into the cortico-cortical interactions that underlie the summated cortical ECFs comprising the ECoG. Such insight is relevant for a synoptic understanding of major state changes in the brain that are diagnosed in clinical practice by visual inspection of the ECoG.

Keywords

EEG; epilepsy; log normal distribution; power law; synchronization

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Conflict of interest
None.

Introduction

The electroencephalography (EEG) of Richard Caton (Caton, 1875) and Hans Berger (Berger, 1929) perhaps constitutes the earliest investigative window on the living brain of continuing importance today. For neurologists, EEG remains crucial to the diagnosis and management of epilepsy and sleep disorders; for neurobiologists, EEG offers insight into brain function at multiple tiers of neural organization. The term ‘EEG’ conventionally denotes the macroscopic scalp recording of time-dependent voltage fluctuations arising from summated electrotonic activity from cortical surfaces of areas $\approx 6\text{--}10\text{ cm}^2$ or more (Cooper et al., 1965; Tao et al., 2005); electrocorticography (‘ECoG’) refers to recordings directly from the cortical surface or intracerebrally at much greater spatial resolution (Kahane and Dubeau, 2014). To the naked eye, the EEG or ECoG appears as a dynamic, mixed-frequency rhythm, whose power spectrum exhibits maxima at the well-known Berger frequencies – delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–25 Hz), etc. (Chang et al., 2011). These spectral peaks, or modes, exist within a monotonic decreasing continuum of ‘arrhythmic activity’ (He et al., 2010) that spans at least five orders of magnitude (Buzsaki and Draguhn, 2004). The identity of the processes that generate arrhythmic behaviour and their relationship to the spectral peaks remains an open question.

The broadband nature and monotonicity of the mode-subtracted EEG spectrum has been interpreted, for instance, as evidence for power-law behaviour (He et al., 2010; Miller et al., 2009; Milstein et al., 2009) – relationships of the form $P(f) \sim f^{-\beta}$, where P , f are spectral density and frequency respectively and β is a number (usually in the range 1–4). Power law interpretations of neural systems have attracted controversy (Touboul and Destexhe, 2010), though they carry theoretically interesting implications if true. A different feature of both the rhythmic and arrhythmic regimes of the EEG is ‘frequency nesting’ (or cross-frequency phase amplitude coupling (Canolty et al., 2006)), which are correlative relationships between the phase of lower-frequency waveforms and the amplitude of higher frequencies. For brain systems composed purely of periodic oscillations frequency nesting is well-understood (Jensen and Colgin, 2007); the origin of nesting in arrhythmic systems is less clear (He et al., 2010). Finally, and despite the large literature in the area, few studies extend their generative hypotheses for the baseline spectrum to explain large-scale state changes in the brain, such as those related to the sleep-wake cycle, or the pathological synchrony defining epileptic seizures.

In this work we use the high fidelity clinical datasets available to us from long term recordings in epilepsy patients undergoing intracerebral EEG (i.e., ECoG) recordings to propose a novel, unified, and parsimonious statistical description of the resting ECoG that synthesizes and reconciles a number of previous observations. The model also provides a conceptual bridge to understanding the transition from baseline EEG/ECoG to several epilepsy-related phenomena described in our previous work – the background rhythms of temporal lobe epilepsy (Kalamangalam et al., 2014a), afterdischarges (Kalamangalam et al., 2014b), and periodic lateralized epileptiform discharges (Kalamangalam and Slater, 2015).

Methods

Subjects

Ten patient subjects (denoted S1–S10; 3 males, 7 females; median age 29 years) were studied. All subjects had refractory focal epilepsy for which invasive monitoring with subdural grid electrodes (SDE; eight subjects) or stereoelectroencephalography (SEEG; two patients) was deemed necessary for seizure onset localization and eloquent function mapping prior to resective brain surgery. Details on the electrode implantation schemes appear as Supplementary Table S1 in the Supplementary Information. The study was approved by the Institutional Review Board of the University of Texas Health Science Centre.

ECoG recording

SDEs were platinum-iridium discs with 3.5 mm in contact with the pia and 10 mm interelectrode distance, embedded in silastic (PMT Corporation, Chanhassen, MN). Sets of 4–40 electrodes forming rectilinear grids or strips were placed under direct vision at craniotomy. SEEG electrodes (PMT Corporation, Chanhassen, MN) were flexible polyurethane wires of outer diameter 0.8 mm, incorporating cylindrical platinum-iridium electrodes of length 2 mm with 1.5 mm gap between contacts. Numbers of contacts per electrode varied from 8–16 and electrodes were placed using a robot-assisted stereotactic technique (Rosa; MedTech, Montpellier, France). Location and numbers of electrodes implanted were determined solely by clinical criteria and all surgical procedures were performed by a single surgeon. The total number of electrode contacts was 1309 ($n = 1309$); contacts per patient varied from 90–192 (mean 131). Cortical surface reconstructions were created from pre-implantation cranial MRI utilizing BrainSuite (Shattuck and Leahy, 2002; Woods et al., 1998a; Woods et al., 1998b). Postoperative cranial CT scans were co-registered with pre-implantation cranial MRI and visualized on the cortical surface reconstructions to ascertain electrode positions using Curry (Compumedics USA, Charlotte, NC). Patients subsequently underwent several days of continuous video-EEG monitoring for recording of seizures (Nihon-Kohden, Inc., Foothills Ranch, CA; EEG sampling frequency was 200, 500 or 1000 Hz, corresponding to analogue data pre-filtered in the passbands 0.08–70 Hz, 0.08–120 Hz and 0.08–300 Hz respectively) before the electrodes were removed via a second surgical procedure.

Data pre-processing

Segments of raw ECoG data in the resting awake and asleep states were reviewed offline in bipolar and referential montages by the first author, a board-certified electroencephalographer. Channels exhibiting seizure onsets, spiking or pathological slowing at any time earlier or later in the multi-day recording were excluded. Three epochs each in the awake and asleep states were chosen from the remainder of the channels from each patient. Epochs were 5–7 minutes long and no closer than eight hours of recording time apart and also more than four hours prior to, or following, any seizure; concurrent review of video and scalp EEG data (if the latter had also been applied) confirmed the behavioural state as either awake or asleep throughout individual epochs. The aggregate of channels across all ten subjects achieved a reasonable representation of the major lobar locations of

the right and left hemispheres, though the brain regions sampled by the chosen channels varied from patient to patient (depending on the electrode placement scheme and exclusion of diseased channels). Chosen epochs were subjected to independent blinded review by another author (JDS), also a board-certified electroencephalographer, who re-marked all the epochs as awake or asleep, and commented on any pathological activity. There was complete agreement between the two reviewers for all the epochs.

Data analysis

Modelling of spectrum amplitude—ECoG epochs were transferred to an average reference montage and analysed with Matlab (The Mathworks, Natick, MA). Each *epoch* was split into 25s long contiguous *segments* yielding 12–17 segments per epoch. The amplitude spectral density of each segment was computed as the square root of the power by the Welch periodogram method (Karl, 1989), in the [1–50] Hz frequency range using a Hamming window and a fast Fourier transform of 2^{16} points. The spectral amplitude was normalized to unity, recomputed through linear interpolation on a logarithmic frequency scale and fit to a five-component Gaussian mixture model (Matlab Statistics Toolbox). Each Gaussian component of the model was parameterized by the amplitude A , the mean μ (i.e., position along the frequency axis) and the standard deviation σ . The multicomponent model pertaining to a particular wake data segment was thus represented by the 15-parameter set $S = \{A_i, \mu_i, \sigma_i, i = 1, 2, 3, 4, 5\}$, for both the wake (S_w) and sleep (S_s) epochs. Goodness of fit for the individual segments was assessed by coefficient of determination (R^2) values. Figure 1 illustrates the modelling sequence on an example data segment. Due to each data epoch comprising several segments, each epoch was associated with multiple (and consecutive in time) S_w or S_s parameter sets. Thus, for each patient we obtained a distribution of parameters sets for wake and sleep that were statistically compared (Table 1). To enable the comparison of Gaussian mixture log-normal model used here with the cited literature, segment spectra were also transformed to log-log coordinates and modelled with straight line fits (Figure 1). The same segment-epoch approach was taken: each segment was transformed to log-log coordinates using logarithmic binning, and the spectral amplitude data fit with a straight line. Power law exponents, denoted β_i , were derived to simply be the slopes of the straight line fits.

Statistical analysis—For each patient we obtained distributions of parameters for both the Gaussian and linear model, for both the wake and the sleep epochs. The median values of each parameter of the models were compared with the Wilcoxon test (Table 1). To account for multiple comparisons we used the Bonferroni correction for the probability of null hypothesis (i.e., $p = 0.05/15 = 0.0033$ for the semi-log Gaussian model that had 15 parameters, and $p = 0.05/2 = 0.025$ for the log-log linear model). We also compared the goodness of the fit (R^2) for the wake and sleep states, for both the semi-log Gaussian model and log-log linear model (Table 2).

Modulation index of phase-amplitude coupling—Cross-frequency phase-amplitude coupling was assessed by using a modulation index (MI) based on the entropy of the distribution of instantaneous amplitude of high frequencies (1–100 Hz) with respect to the instantaneous phase of the low frequencies (1–20 Hz), using the methods detailed in He et.

al. (2010). We computed the instantaneous phase in 20 bins of 1 Hz each, and the instantaneous amplitude in 20 bins of 5 Hz each, for successive intervals of 100s. MI was then transformed in a Z -score (MI Z -score) by using the mean and the standard deviation of the MI corresponding to surrogate data obtained by random shuffling. For each pair of binned amplitude and phase, we computed the significance of the MI by using the p -value derived from the Z -score together with the Bonferroni correction for multiple comparisons. Finally, for each patient and time epoch of 300 sec, the percentage of electrodes having significant phase-amplitude coupling was computed.

Results

Curve fits

Figure 2 demonstrates the fit of the mixed log-normal model on eight randomly chosen datasets (electrodes) from different patients and over different brain regions over both the right and left hemispheres (Figures 2A–D). The R^2 values are uniformly high, and the model is seen to fit the entirety of the spectrum from the lowest frequencies to beyond 30 Hz. Table 2 provides a listing of the channel average of R^2 values for all 10 patients. Due to the large total number of time segments per electrode, and, correspondingly, large number of models, we show for each electrode in Figure 2E only the model having the median R^2 value.

Sleep-wake differences

Figures 3A–C include the mean model coefficients A_1 – A_5 , the means of Gaussians, μ_1 to μ_5 , computed in frequency units (e.g. 10^{μ_1} to 10^{μ_5}) and the dispersion of the Gaussians, σ_1 to σ_5 , also computed in frequency units (10^{σ_1} to 10^{σ_5}), for the wake and sleep states of the subject S1 (as an example). The central difference between the wake and sleep models is in the height (amplitude) of the individual Gaussians, with only minimal change in the location of the maxima or variance. Thus, the same model – with Gaussian amplitudes redistributed – fits both the wake and sleep semi-log spectra. Table 1 provides results of significance testing. We speculate on the neurophysiology underlying this simple yet striking finding in the Discussion.

Phase-amplitude coupling

The presence of a systematic relationship between the phase of low frequency oscillations and the power of higher frequency activity across the whole ECoG bandwidth was demonstrated by He and colleagues (2010). This feature was seen in our data as well. Figure 4 illustrates the instantaneous phase-amplitude coupling for two subjects S4 and S7, and for both wake and sleep state. In all subjects we observed a high percentage of electrodes showing phase-amplitude coupling in the majority of analysed 100s time intervals, irrespective of the wake and sleep state.

Epilepsy-related transformations

The log-normal model is a continuum approximation in frequency space: the ECoG is viewed as a collection of oscillators whose frequency distributions (via a combination of intrinsic frequencies and other frequencies arising from self-interaction) approximate that statistical distribution. We have demonstrated previously (Kalamangalam et al., 2014a;

Kalamangalam et al., 2014b; Kalamangalam and Slater, 2015) that such a formalism for the EEG and ECoG – a continuum hypothesis, though not necessarily restricted to a particular distribution – naturally lends itself to the emergence of large-scale synchronous (i.e., epileptic) activity. Synchronization involves the oscillators ‘condensing’ to a smaller distribution by increasing their mutual coupling, leading to the appearance of large amplitude coherent rhythms in the time domain as the coupling parameters cross a threshold. Figure 5, adapted from Kalamangalam et al. (2014b) illustrates the idea; see also Figure 6.

Discussion

A major theme in today’s systems neuroscience is the characterization of the brain’s ‘resting’ state, whether through imaging (resting state fMRI) or electrophysiological (EEG/ECoG, magnetoencephalography) methods. The growing interest in the resting state is due in part to the observation that in a variety of experimental paradigms brain patterns following ‘activation’ appear only a little different from the baseline activity in the absence of activation (Sporns, 2011). Thus, the functional and computational repertoire of the active brain appears to be implicit in, derivable from, or a variation of, the properties of the resting brain, itself a complex multidimensional dynamical system. Statistical modelling provides a low-dimensional parametric abstraction of the resting state ECoG; its deeper value however derives from the generative mechanism(s) the particular density function employed suggests. For instance, the large range of frequencies (≈ 5 orders of magnitude) of the resting ECoG implies a slowly-decaying (or ‘heavy-tailed’) density, raising the possibility of a power law distribution $P(f) \sim f^{-\beta}$ (Newman, 2005). Power laws with $\beta > 1$ do not have a well-defined mean, and with $\beta > 2$ do not possess a well-defined variance. These features have an intuitive appeal as models of brain behaviour: time-scale freedom can be thought of as the physical instantiation of long-term ‘memory’; the lack of a well-defined variance as an extensive repertoire of possible dynamics.

The motivation for this work was somewhat different in arising from the everyday clinical practice of epilepsy. For electroencephalographers habituated to the classical Berger (α , β , δ , etc.) EEG/ECoG rhythms that transition dramatically between the sleep-wake state and seizure onset and offset, a fundamental question regarding the resting state is: how is the underlying cerebral fabric organized for these transitions to take place? That is, what description of the resting baseline EEG/ECoG can be adapted with regard to the known physiology to also account for these profound state changes? It is clear that both sleep-wake and seizure transitions take place in healthy brain: everyone sleeps for a portion of the day, and though the seizures of partial epilepsy arise from a delimited focus or network, they readily invade the rest of the brain (secondary generalization). It is also clear that several of the Berger bands have distinct anatomical ‘generators’: for instance the ‘slow’ (< 1 Hz) oscillation that arises from isolated cortex, ‘clockwork delta’ that arises from the thalamocortical system, and sleep spindles that arise from the reticular thalamus (Amzica and Lopes da Silva, 2011). The electrophysiology of sleep is entirely described by changes in these canonical oscillations (Chang et al., 2011). Similarly seizures, when viewed in the conventional passband (0.5–70 Hz), are oscillatory transitions: rhythmic activity that evolves from the background in space and time (Koubeissi and So, 2014). Importantly, the rhythm of a fully developed seizure, or of slow-wave sleep, dominates all the other rhythms – it is as if

the seizure or sleep state ‘enslaves’ the baseline scatter of frequencies into a smaller ‘master’ set. Such a scenario – the organization of spatiotemporally separate but interacting dynamic elements into global patterns – has been studied for decades in diverse fields (Kelso, 1995; Kuramoto, 1984; Strogatz, 2003; Winfree, 2001). We adopt this ‘synergetic’ (Haken, 1984) perspective in this work, hypothesizing the background EEG/ECoG itself as a massive set of coupled oscillators with its ensemble dynamic behaviour (wake, sleep, seizure, etc.) dependent on variation in physiological parameters (e.g. inter-oscillator interactions and external influences). That is, we modelled the entirety of the ECoG spectrum as oscillation based, fusing the ‘rhythmic’ and ‘arrhythmic’ regimes.

An important choice from a data-processing point of view was our modelling of the *amplitude* spectrum, rather than the *power* spectrum. This arose from our interest in modelling the ECoG time-series signal itself, rather than its spectral or autocorrelation characteristics. That is, if an ECoG signal $S(t)$ epoch were expressed as the Fourier series

$$S(t) = \sum_{n=0}^{\infty} a_n \cos n2\pi f_0 t + b_n \sin n2\pi f_0 t \stackrel{\text{def}}{=} \sum_{n=0}^{\infty} A_n \cos(n2\pi f_0 t + \varphi_n),$$

our aim was to model the distribution of $A_n = \sqrt{a_n^2 + b_n^2}$, the amplitude of each sinusoidal component, rather than the power A_n^2 . Clearly, if the power spectrum followed a statistical power law distribution $\sim f^{-\alpha}$, so would the amplitude spectrum ($\sim f^{-\alpha/2}$); thus the presence (or not) of statistical power law behaviour would be unaffected by the choice of modelled variable.

At a conceptual level, our oscillation-based spectrum hypothesis conflicts with the literature that views the ‘rhythmic’ and ‘arrhythmic’ regimes of the EEG as distinct phenomena. Milstein and colleagues (2009) fit a power law with exponent $\beta \approx 2$ to field potential power spectra obtained with microwire local field potential recordings in humans. Though the spatial scale of their recording cannot be directly compared with our ECoG recordings with clinical macroelectrodes, these authors did observe Berger peaks in their spectra. However, their analysis deliberately chose epochs with absent periodicities (e.g., suppressing the alpha rhythm by keeping the eyes open). In contrast, our data always led to spectra with at least one local maximum, usually in the region of 1 Hz. Miller and colleagues (2009) fit a power law with $\beta \approx 4$ to human subdural grid ECoG power spectra above 80 Hz; a more elaborate iterative method was used to arrive at a hybrid formula spanning the range 15–195 Hz that yielded $\beta \approx 2$ at frequencies below ≈ 75 Hz, and $\beta \approx 4$ for higher frequencies. These authors did not consider frequencies lower than 15 Hz due to interference from the Berger peaks. In contrast, we have focussed on *exactly* the Berger bands, demonstrating that they may be subsumed into a unitary description of the entire spectrum within our bandwidth. He and colleagues (2010) report on human subdural grid electrode ECoG, using recording bandwidths comparable to ours (0.1–100 Hz) and using power-law curve fits to power spectra. These authors also subtracted the periodic components from their spectra prior to analyses that demonstrated $\beta \approx 2$ for the majority of their bandwidth. For signals composed of fixed modes, continuous-appearing spectra can artifactually arise as a consequence of the ‘uncertainty principle’ of limited signal length (Karl, 1989); increasing signal length reveals

previously-hidden (and static) periodic elements in the spectrum. He and colleagues applied this approach to marshal evidence for arrhythmic behaviour in the ECoG: spectra evaluated for as long as 83 minutes showed no new periodicities that were not evident at 20s data lengths. This demonstration however did not address the possibility of time-varying frequencies. Indeed, studies that observe the Hilbert phase of ECoG signals uniformly report its dynamic nature, arguing that even narrow-band EEG modes are constantly shifting in frequency (Nunez and Srinivasan, 2006). Such a scenario is only natural in a system subject to constantly fluctuating environmental drive (Whittington et al., 2010). In such a case, increase of data length would improve spectral resolution but not unearth new periodicities.

The comparable R^2 between power law fits and our log normal model over some of the frequency range raises the question of how both formulations can be equivalent fits to the data. In fact, the debate of ‘power law versus log normal’ is an old one in statistics, and their similarity can be understood simply (Mitzenmacher, 2004) by appreciating that the log-normal function has the form of a quadratic in log-log coordinates (see Supplementary Information). Figure 7A illustrates this point with a linear approximation to a quadratic with suitably chosen parameters; the linear fit is virtually indistinguishable from the quadratic over $O(1)$ range. The latter order of variation in the logarithm translates to $O(10^{O(1)})$ variation in the native frequency variable, which is in fact the range of frequencies modelled in the literature (He et al., 2010; Miller et al., 2009). Thus, it is no surprise that ECoG data fit either model. However, we emphasize our preference for the log normal formulation due to its ability to model the lower end of the spectrum that includes the Berger bands into a unitary description of the entire spectrum. In other words, a quadratic fit in log-log coordinates would be expected to perform better than a straight line, which is indeed observed (Figures 7B–C).

A different question concerns the genesis of the log normal distribution itself. Log normal distributions arise naturally from multiplicative growth processes abundantly observed in biological, ecological and economic systems (Limpert et al., 2001). One may speculate that a statistically similar multiplicative growth process underlies the maturation of the cerebral cortex from infancy onwards. Support for such speculation comes from, for instance, the discovery of non-random log-normal patterns to connectivity strengths in the rat cerebral cortex (Song et al., 2005), with sparse strong local connections immersed in a ‘sea’ of weaker more broadly distributed connections. Thus, the composite ECoG may be imagined to arise from large numbers of distributed connections giving rise to the slower rhythms, and smaller numbers of local connections underlying faster frequencies. Factoring in multiplicative interactions between established rhythms would generate further sets of frequencies that could also contribute to the overall picture. This scenario is similar to the views of Whittington and colleagues (2010), where a process of ‘concatenation’ (iterative addition) of elementary frequencies reproduces a continuous spectrum. We do remain aware however that minor variations in the generative process for the log-normal can give rise to alternative distributions, such as the power law or double-Pareto distribution (Mitzenmacher, 2004). An attractive feature of the latter distribution is that it can be approximated by two different power laws for two regimes of the frequency variable, and thus potentially yield the ‘knee’ or ‘shoulder’ of the spectra described by some authors (He et al., 2010; Miller et al., 2009).

Comparison of the wake and sleep ECoG spectra in our dataset revealed that the two states differed essentially in the distribution of amplitudes accorded to their respective Gaussian models. This finding, simple, striking and highly statistically significant, suggests the following phenomenological view of the sleep-wake transition. Consider the waking brain's multifarious and parallel activities of perception, action and thought, which might be imagined to require multiple operations in diverse brain circuits of varying spatial scale. The mix of rhythms in the ECoG would reflect this variety. In sleep, these same systems are organized differently due under the modulatory influences of sleep promoting brain systems (Steriade, 2009); influences that favour long-range synchronous interaction rather than local circuits. The power in the aggregate signal therefore would migrate to the lower end of the spectrum. Though severely simplified, such a view promotes a continuum view of the sleep wake transition, as the networks of the brain shift in their relative spatiotemporal emphasis. At the macroscopic clinical level, this is certainly what is observed: the EEG rhythms of wakefulness gradually give way to the rhythms of sleep: the alpha rhythm slows and drops out, slower frequencies gradually become more prominent, novel frequencies (e.g. sleep spindles) emerge, and eventually a large amplitude relatively monomorphic rhythm (slow-wave sleep) prevails. The structure of our model naturally captures this transition, in contrast with the study of He and colleagues (2010) that failed to observe statistical significance between the state of arousal and the exponent of the power law fit of the spectra.

'Nesting' or cross-frequency coupling refers to systematic relationships between the slower and faster frequencies of the mixed frequency EEG/ECoG. A particular form of nesting – phase-amplitude coupling (PAC), wherein the power in the gamma band of the ECoG is locked to the phase of the concurrent theta oscillation – was described in band-passed human ECoG by Canolty and co-workers (Canolty et al., 2006). Such a mechanism can be explained simply by considering the slower frequency modulating the level of excitability of the principal units of local circuits; coordinated discharges of groups of principal units occur as they are taken over threshold by the slower rhythm, creating bursts of local gamma power in the ECoG (Jensen and Colgin, 2007). The study of He (2010) however demonstrated extensive PAC in the background ECoG, even within the arrhythmic regime, the explanation for which was left open by the authors. If one however considers the entire ECoG as oscillation based - as we do - the appearance of PAC across the broader bandwidth is less perplexing.

Despite the focus on the log normal model in this work, our conclusion is a more general one: that the entirety of the ECoG (spectral peaks plus the arrhythmic regime) may be modelled as a concatenated continuum, at least for the bandwidth (<50 Hz) studied here. This bandwidth is small compared to that of the overall ECoG, but it possesses the majority of the power of the spectrum; it is also in this small bandwidth that several physiological and pathological phenomena achieve their clinical interest. We have deployed the oscillator continuum formalism in previous work with clinical data, where increasing coupling strength between the oscillators leads to large-amplitude synchronous rhythms that model afterdischarge (Kalamangalam et al., 2014b) and lateralized periodic discharge (Kalamangalam and Slater, 2015). Figure 5, reproduced from the former citation, illustrates this relationship of frequency 'condensation' between the baseline ECoG at an electrode and an afterdischarge at that same location following electrical stimulation. Importantly, the

appearance of a synchronous rhythm does not depend on the initial shape of the spectrum, only that the inter-oscillator coupling is sufficiently strong. We thus understand how a rhythm may ‘emerge’ from a featureless arrhythmic background, as in the observation of He et. al. (2010) (Figure 4D of their paper: an 8 Hz oscillation emerges transiently from an arrhythmic baseline accompanying a motor task). To illustrate this further, we return to the Kuramoto model (Kuramoto, 1984; Strogatz, 1994) used in Kalamangalam (2014b); see Supplementary Information for details. Figure 6A shows a short section of a mixed frequency time series whose amplitude spectrum (Figure 6B) is broadband (i.e., arrhythmic) between 2–14 Hz and lacking a clear dominant peak. The parameter K in the Kuramoto model represents the strength of the coupling between the frequencies; as K is increased from zero (i.e., the uncoupled state) past a threshold, the aggregate mixed frequency rhythm becomes synchronous at ~8 Hz, an intermediate frequency. Figure 6C shows this ensemble oscillation for a value of K above synchronization threshold; the amplitude spectrum now exhibits a peak (Figure 6D) that has arisen from within the baseline band.

The statistician George Box’s famous assertion that ‘all models are wrong’ (Box, 1976) must also be true of ECoG models. Nevertheless, the observations of generations of electroencephalographers regarding the stereotypic and often simple-looking transformations in human EEG suggest that a phenomenological description may be successful. Despite the small number (10) patients studied in this work, a continuum model of the ECoG spectrum is suggested that synthesizes some prominent features of, and transformations between, the wake, asleep and epileptic EEG. These ideas in turn suggest how the cellular elements of cortical tissue may self-interact during different brain states, or conversely, how modes of self-interaction by parametric variation *yield* brain states. Important extensions of the current work will be to explore the continuum hypothesis under conditions of controlled motor or cognitive activation, or under electrical stimulation paradigms relevant to emerging neuromodulation therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. A statistical model of the spectral profile of the human electrocortigram (ECoG) is proposed.
2. The model synthesizes several previous observations and conjectures regarding ECoG structure.
3. The model extends to the transition to certain epileptic behaviours, as well as sleep-wake changes.

Figure 1.

The Gaussian mixture and power-law model for an example ECoG. A: Surface reconstruction of the medial aspect of the left hemisphere of subject S9 highlighting a single randomly-chosen location (starred) over the premotor area. This location was identified by co-registering the patient's post-implant CT scan with the pre-operative MRI scan and knowledge of the implant scheme (numbers and type of electrodes used; see text). B: Typical 10-s ECoG epochs from the example electrode location, illustrating their raw appearances in wakefulness and sleep. *x*-axis: time (seconds); *y*-axis: voltage (μvolts). The sleep waveforms are of higher amplitude but of smaller spectral bandwidth. C: Modelling of the wake spectral amplitude. The normalized *spectrum* (top left) in the interval 1–50 Hz (grey line) was smoothed (black line) and recomputed on a logarithmic frequency scale. The resulting *semilog spectrum* (top right, grey line) was modelled as a composite multimodal function (black line; $R^2 = 0.82$). The latter arises from five individual Gaussian components (bottom left, grey lines) that summate to yield the composite (black line). The amplitude spectrum was also transformed to log-log coordinates to yield the *log-log spectrum* (bottom right, grey line) that was fit with a linear model (black line; $R^2 = 0.74$). D: An identical modelling

sequence for the sleep ECoG. In contrast to the wake state, the Gaussian and linear models yield comparable R^2 values.

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Figure 2.

Modelling of the amplitude spectrum in wakefulness and sleep over multiple brain regions. A–D: Medial and lateral brain surface templates, displaying a collage (black dots) of all brain electrode locations sampled from the entire patient group. Each black dot represents an electrode location sampled at least once, in one or more patients. Representative ECoG epochs were chosen from circled locations 1–8, each from a different patient, and over the medial and lateral surfaces of both hemispheres. The starred location was used in Figure 1. E: Eight panels, each with a wake (top) and sleep (bottom) model, from the eight chosen

electrode locations. The panel titles pertain to the subject, electrode and sleep-wake state, such that, for example, 'S6/E5/Sleep' represents subject S6, electrode location 5 on the collage, and in the sleep state. Semi-log spectra (grey lines) are modelled with the sum of a Gaussian mixture (black lines). Each electrode was associated with multiple models, as the analysis was repeated for consecutive time intervals of 25 sec (see text). Shown here the models corresponding to the median parameters; the median R^2 is seen to be uniformly high. See also Table 2.

Figure 3.

Comparison of wake and sleep Gaussian models in a typical case (subject S1). A: The amplitudes of the Gaussian functions in the model (A_1 to A_5) are all significantly different for wake (grey bars) and sleep (black bars) (Wilcoxon test with Bonferroni correction for multiple comparisons, $p < 0.003$). B: The means μ_1 – μ_5 - that indicate the position of the maximum of the individual Gaussians (shown here in native frequency units, e.g. μ raised to the power 10) - differ less between the awake and sleep states. The same is true for the dispersions σ_1 – σ_5 , shown in (C) in frequency units (see also Table 1). Thus, from a modelling perspective, the essential difference between the wake and sleep states is the amplitudes of the Gaussians, not their location or dispersion. D: Comparison of the semi-log Gaussian mixture model with the log-log linear model, aggregated for all the subjects. R^2 values during wakefulness are significantly better ($p < 0.05$, two-tailed t-test) for the log-normal model; differences during sleep are not statistically significant.

Figure 4.

Phase-amplitude coupling between low and high frequencies computed over a time epoch of 300 seconds, during both wakefulness and sleep. A–C: The percentage of electrodes exhibiting significant phase-amplitude coupling for subject S4. B–D: Similarly for subject S7.

Figure 5.

Example of the ‘condensation’ relationship between the baseline electrocorticogram and the ensuing afterdischarge (AD) following supra-threshold stimulation, reproduced from Kalamangalam et. al. (2014b). A: an 8-second baseline ECoG epoch from a single electrode contact. B: the power spectrum of the baseline epoch is an irregular mix of components that is biased towards the lower frequencies. *x*-axis: frequency (Hz); *y*-axis: power spectral density ($\mu\text{volts}^2/\text{Hz}$). C: an 8-second AD appears at the same electrode following electrical stimulation. D: The AD’s power spectrum is a ‘condensed’ version of the baseline spectrum: less spread out, more sharply peaked, and of much greater amplitude at the maximum, as if the spectral modes comprising the baseline had coalesced towards a common average. Thus, conceiving the baseline spectrum as a distribution of oscillatory components implies that epileptiform change is a continuous transition in the distribution, characterized by coalescence towards a common average. In the time domain, such a process yields the high-amplitude synchronous waveform characteristic of AD.

Figure 6.

Numerical results from simulation of the Kuramoto model with $N=250$ oscillators. A: Time series for 10 seconds of simulated time with all oscillators uncoupled. x -axis: seconds, y -axis: voltage amplitude (arbitrary units). The simulated ECoG is polymorphic and appears irregular, with a broadband amplitude spectrum (B) that lacks a single well-defined maximum. C: Increasing the coupling from zero to above threshold yields a highly synchronous, large amplitude waveform. Its amplitude spectrum (D) consists of a single dominant frequency (i.e., a rhythm) that arises from the middle of the baseline broadband mix (i.e., an arrhythmic regime).

Figure 7.

Comparison of quadratic and linear data fits. A: An example quadratic $\log A = -0.5 - \log f - 0.5 (\log f)^2$ and its linear approximation $\log A = 0.25 - 2.25 \log f$ at (1, -2) are practically indistinguishable over the range [0.75, 1.75]. However a linear fit on a log-log plot implies a power law in the native variables, whereas a quadratic, a log-normal law (see Supplementary Information). B: A straight line fit to the 6–30 Hz segment of the awake amplitude spectrum in log-log coordinates of subject S9 (taken from Figure 1). The linear fit fails to capture the

bow of the curve, in contrast to the quadratic (C) that yields higher R^2 values. This suggests a log-normal, rather than a power-law, distribution of the native variable.

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Table 1

Comparison of the coefficients of the Gaussian mixture model for wakefulness and sleep.

Subjects	A ₁	A ₂	A ₃	A ₄	A ₅	μ_1	μ_2	μ_3	μ_4	μ_5	σ_1	σ_2	σ_3	σ_4	σ_5
S1	1	1	1	1	1	0	1	1	0	1	0	0	1	0	0
S2	1	1	1	1	1	1	0	1	1	1	1	1	0	1	0
S3	1	1	1	1	1	1	1	1	1	1	0	0	1	0	1
S4	0	1	1	1	1	0	1	1	0	1	0	0	0	0	0
S5	1	1	1	1	1	0	0	1	1	1	0	1	1	1	1
S6	0	1	1	0	1	0	1	1	1	1	1	0	1	1	0
S7	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1
S8	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
S9	1	1	1	1	1	1	0	1	0	1	1	0	1	1	1
S10	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1

Cells indicated by '1' represent significantly different model coefficients for wake and sleep (Wilcoxon test with the Bonferroni correction, $p < 0.003$ – see Materials and Methods). Cells indicated by '0' denote no statistically different differences.

Table 2

Goodness of fit for the Gaussian mixture and linear models.

Subjects	Gaussian model		Linear model	
	R^2 wake	R^2 sleep	R^2 wake	R^2 sleep
S1	0.814	0.858	0.811	0.913
S2	0.798	0.870	0.624	0.838
S3	0.790	0.854	0.724	0.878
S4	0.768	0.800	0.731	0.800
S5	0.778	0.836	0.642	0.820
S6	0.754	0.792	0.686	0.782
S7	0.796	0.849	0.732	0.849
S8	0.837	0.897	0.856	0.947
S9	0.784	0.889	0.716	0.910
S10	0.805	0.864	0.785	0.907

Median coefficients of determination for both wake and sleep states, for both classes of models. Wake R^2 values are uniformly high, and superior for the Gaussian model compared to the linear model; both models yield comparably high R^2 values in the sleep state. See also Figure 3.