ENTROPIES OF THE EEG: THE EFFECTS OF GENERAL ANAESTHESIA.

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The aim of this paper was to compare the performance of different entropy estimators when applied to EEG data taken from patients during routine induction of general anesthesia. The question then arose as to how and why different EEG patterns could affect the different estimators. Therefore we also compared how the different entropy estimators responded to artificially generated signals with predetermined, known, characteristics. This was done by applying the entropy algorithms to pseudoEEG data:
(1) computer-generated using a second-order autoregressive (AR2) model,
(2) computer-generated white noise added to step signals simulating blink and eye-movement artifacts and,
(3) seeing the effect of exogenous (computer-generated) sine-wave oscillations added to the actual clinically-derived EEG data set from patients undergoing induction of anesthesia.

BACKGROUND

ARE EEG ENTROPY ESTIMATORS PURELY AN ELEGANT METHOD OF SIGNAL PROCESSING?

What is entropy?
Claude Shannon developed the modern concept of 'information' or 'logical' entropy as part of information theory in the late 1940s(Shannon CE 1948). Information theory dealt with the nascent science of data communications. Shannon entropy (H) is given by the following equation:

$H = -\Sigma p_k \log p_k$, where p_k are the probabilities of a datum being in bin k.

It is a measure of the spread of the data. Data with a broad, flat probability distribution will have a high entropy. Data with a narrow, peaked, distribution will have a low entropy. As applied to the EEG - is entropy merely just another statistical descriptor of the variability within the EEG signal (comparable to other descriptors, such as the spectral edge, of the shift to low frequencies that occurs on induction of general anesthesia)?

Part of the answer to this question lies back in the original definition of thermodynamic entropy in the nineteenth century by Clausius and others. The change in thermodynamic

entropy (*dS*) of a closed system is defined as a quantity that relates temperature (*T*) to the energy (= heat, *dQ*) transferred to the molecules via the equation:

$$dS = dQ/T$$

Because entropy changes with change of state (e.g. solid to liquid), and because entropy tends to increase with time, it can be considered to be a measure of the degree of 'disorder' of the system. However, 'disorder' is a loosely defined term. Boltzman showed that thermodynamic entropy could be defined precisely as (Boltzman's) proportionality constant (*k*) multiplied by the logarithm of the number of independent microstates (*W*) available for the system:

$$S = k \log (W)$$

Because he was able to explain the changes in macroscopic observables (such as temperature), from the changes in kinetic energy of a collection of individual molecules - he thus pioneered the science of statistical mechanics. Thermodynamic entropy has a well-established physical basis. It is possible to derive the Shannon/'information' entropy (*H*) from the thermodynamic Boltzman formula (*S)*. However it must be clearly stated that, because there exists a formal analogy between *H* and *S*, it does **not imply** that there necessarily is a material basis for equating *H* and *S* in regards to the cortical function. Nevertheless there does exist tantalizing neurophysiological evidence that the utility of information entropy estimators as measures of cortical function is because - as the cortex becomes unconscious - a true decrease in (the logarithm of) the number of accessible microstates (*S*) occurs at the neuronal level (Steyn-Ross et al. Towards a theory of the general anesthetic-induced phase transition of the cerebral cortex: 1. A thermodynamics analogy, and 2. Numerical simulations, spectral entropy, and correlation times. Phys Rev E, *in press*),(John, Easton et al. 1997; Micheloyannis, Arvanitis et al. 1998; Steyn-Ross 1999.; Quiroga, Arnhold et al. 2000). If this is true, it means that the change in information entropy within the EEG may window a real change in cortical functional organization. Thus the term 'entropy' may be more than merely a statistical measure of EEG pattern, but may in some way truly reflect the intra-cortical information flow.

Entropy is the logarithm of the number of ways that the microstate can rearrange itself and still produce the *same* macrostate. In thermodynamics, the microstate is the momentum and position of each molecule. The difference between true thermodynamic entropy and other information entropies is that the distribution of the *kinetic energy* of individual molecules is not necessarily involved in information entropy estimators. The ‘energy’ has been abstracted away from heat energy and thermodynamics, and can mean any change in the activity of the ‘particles’ that make up the system under observation. In this paper the 'energy' is the changes in cortical pyramidal membrane potential - which produce fluctuations in the local field potential of the cortex – which, in turn, are then physiologically and statistically averaged to produce the scalp-measured EEG signal.

What is the significance for the EEG?

If the EEG is to some degree a window on cortical processes, the changes in entropy of the EEG may be expected to indirectly coarsely measure changes in the entropy occurring within the cerebral cortex itself. Assuming that the main function of the conscious cortex is the processing and manufacture of information, it would not be unreasonable that some sort of 'information measure' may be useful. The problem is that (like the word 'disorder'), the word 'information' carries too many other meanings and connotations, and has to be carefully, and scientifically defined to be really useful in this context. Perhaps the simplest, practical, working description of the entropies of the EEG would be - measures of the extent that constraints (in our case, general anesthesia), limit the number of accessible states available to the cortex. This statement is presented without proof, but is consistent with the experimentally-observed changes presented later in this paper. It is clear from this that, whilst it could be expected that increased number of microstates is in general associated with a more 'complex' system, entropy does not itself necessarily directly measure the 'complexity' of a system - which has other implications of variability in response to inputs etc.

If entropy is defined as the logarithm of the number of commonly accessible cortical microstates, the question arises - what are cortical microstates? There is growing neurophysiological evidence that cognitive activity involves the transient formation and dissolution of interconnecting cortical neuronal assemblies (‘activation’ and ‘quiescence’)(John, Easton et al. 1997). It would not be unreasonable to claim that these coherent assemblies are effectively the functional cortical microstates. This activity is manifest in the scalp EEG as a broader-band, 'white-noise' spectrum(Stam, Tavy et al. 1993; Thomeer, Stam et al. 1994).

If,
(1) the state of conscious awareness requires the efficient formation of many cortical microstates, and
(2) if the microstates of the EEG signal reflect in some way the cortical microstates, then the decrease in EEG entropy (as is seen with general anesthesia) is an indicator that there are fewer available cortical microstates(Weiss 1992).

The Cortex-Consciousness Paradox: If you call entropy ‘disorder’, the higher values of entropy found in the EEG from the awake cortex imply that the cortex in the conscious state is more disordered than the unconscious state. This paradox highlights the problems with equating entropy with disorder. At present we lack the means to discern the exquisite high dimensional patterns generated by the conscious cortex during cognition, and call it ‘noise’! This is the reason why we prefer to define entropy in terms of available microstates rather than order. Perhaps a better metaphor would be to describe entropy as 'freedom of choice'. The conscious cortex is free to move to many available microstates.

A VISIT TO THE ENTROPY ZOO

The decrease in complexity of the EEG signal during induction of general anaesthesia is manifest primarily as a change in the underlying slope of the EEG's power spectrum. The parameter commonly used to describe the slope is the Hurst exponent. This parameter is most conveniently estimated using detrended fluctuation analysis (DFA) (Heneghan C and Mcdarby G 2000). Although it is not a true entropy estimator, we have included the DFA as one of the EEG parameters in our methods because it is an easily calculated, robust measure of the autocorrelation structure of the EEG. Recently a number of different entropy estimators have been applied to EEG data attempting to quantify complexity and/or 'depth-of-anesthesia'. These techniques do not measure the shape of the distribution of the EEG voltages per se, but instead describe how the EEG signal changes with time – either in frequency-space or phase-space. They may be therefore loosely classified into two groups.

1) Spectral Entropies

There are various ways of estimating the changes in the amplitude component of the power spectrum of the EEG. These use the amplitude components of the power spectrum as the 'probabilities' in the entropy calculations. Interestingly, by using frequency-space we are defining the microstates in terms of rates-of-change. A wide range of accessed frequencies (a flat spectrum) implies many possible different rates-of-change of summed pyramidal cell membrane potentials.

The prototype of this group is the Spectral Entropy (SEN) (Inouye, Shinosaki et al. 1991; Fell, Roschke et al. 1996). The SEN is the Shannon entropy formula suitably normalised and applied to the power spectral density of the EEG signal.

$SEN = -\Sigma\, p_k \log p_k / \log(N)$, where p_k are the spectral amplitudes of frequency bin k.

$\Sigma\, p_k$=1, and N = number of frequencies. In our paper we have used k from 1 to 47, representing a frequency histogram with 1Hz bins over the range 1-47Hz inclusive. The SEN can take values from zero (if the spectrum contains purely a single oscillatory peak) to one (if the spectrum is that of uncorrelated white noise – ie. $p_k = 1/N$).

The SEN can be shown to be a special case of a series of entropies termed Renyi Entropies (R(α)) (Amari S 1985; Grassberger, Schrieber et al. 1991; Gonzalez Andino, Grave de Peralta Menendez et al. 2000). Their formula is:

$R(\alpha) = -\alpha/(1-\alpha)\, \Sigma \log p_k^{\alpha}. \quad (\alpha \neq 1)$

Taken together a spectrum of these Renyi entropies can be used to define a given probability distribution in a manner similar to the conventional use of statistical moments for the same purpose. In this paper we use only the value of α = -1, which we have termed the Generalised Spectral Entropy (GSE). Because it is a reciprocal transformation, this transformation differs from the SEN in that the sum is weighted towards frequencies with relatively smaller amplitudes. These tend to be those in the higher end of the

frequency band. Thus heuristically, the results from the GSE may not be dissimilar to the SEN calculated over a higher frequency band (eg. 20-45Hz).

The dissimilarity between two probability density functions can be quantified using the Kullback-Leibler entropy (K-L) (Torres ME and Gamero LG 2000) – also sometimes called the 'Relative Entropy', or 'Cross-entropy'(Qian 2001). The K-L has been shown to be essentially equivalent to yet another entropy, the 'Renormalized Entropy' (Quiroga, Arnhold et al. 2000). We will only consider the K-L. It is possible to establish a baseline spectrum (q_k) of the EEG when the patient is awake and then use the K-L to estimate how much it changes when the patient is given anaesthesia and loses consciousness. K-L is simply defined as:

$$K\text{-}L(p|q) = \Sigma\, p_k \log (p_k / q_k)$$

Obviously this technique cannot be instituted halfway through an operation! It does have the possible advantage of individualising the EEG changes to be specific for each patient.

For completeness there are a large number of possibilities of using an entropy estimator to estimate the spread of any measure of EEG patterns. Specifically, we have looked at:

1) The Shannon entropy of the bispectrum, (SENhos),
2) The Shannon entropy of the wavelet spectrum (SENwv)(Rosso, Blanco et al. 2001), and
3) A variant of the spectral entropy, that uses the spectrum of the second derivative of the time series called the acceleration spectrum entropy(Stam, Tavy et al. 1993).
4) A quantity called the Fisher Information (I) (Freiden BR 2000).

$$I = -(\Delta k^{-1}) \Sigma \{[p(k_{n+1}) - p(k_n)]^2 / p(k_n)\},$$

This measure has some interesting properties, and has been termed a 'mother' entropy. Firstly, it is theoretically, complementary to the Shannon entropy (which is a global measure) because I has the property of locality. (ie. if you shuffle p_ks, (I) will be different.) Also I is related to K-L by the following relation:

$I = -(2/\Delta k^2)$ K-L $[p(k),p(k+\Delta k)]$, where Δk is the width of the frequency bin.

Thus I may be considered as being proportional to the cross entropy (K-L) between the PDF $p(k)$ and its shifted version $p(k+\Delta k)$. Heuristically, I is a measure of the absolute gradients within the spectrum.

I is also proportional to the Renyi entropies

$$R(\alpha) = -(\Delta k^2/2)\, \alpha/(1-\alpha)\, I. \quad (\alpha \neq 1)$$

In practical terms none of these three last-mentioned techniques appeared to contribute significant new information to that gained from the other entropy estimators, and thus their results are not reported further.

2) Embedding entropies

The second cluster of techniques are those which directly use the EEG time series. The entropies that incorporate this as part of their calculation are the Approximate Entropy (ApEn), and the entropy of the Singular-Value Decomposition (SVDen). Information about how the EEG signal fluctuates with time is obtained by comparing the time series with itself, but lagged by a specified time interval. This practice is usually technically termed as embedding the one-dimensional signal in a 'phase-space'. Intuitively it seems sensible that, if an EEG signal is irregular, the position of a particular point will not be easily predicted using knowledge of its previous points; whereas in a regular signal the position of the point will be more reliably predicted. The number of previous (lagged) points used in making the prediction is the embedding dimension (m). For a process whose underlying dimension is n (ie. Which can be described uniquely in terms of n parameters), the required embedding dimension is; $m \geq 2n+1$, and the required minimum date size to extract these n parameters is 10^m.

Suppose that the EEG (and by assumption the cortex) was operating under extreme constraints and had a dimension (n) of only 10 (ie 10 parameters could describe the signal), then the *minimum* required data length is $\geq 10^{21}$ points! This exponential dependence of data length on the complexity of the underlying process is called the 'curse of dimensionality' in nonlinear analysis. It is impractical to properly embed the EEG signal. ***Thus these techniques are NOT able to fulfil their theoretical promise and extract high-dimensional information from the univariate EEG data-stream.***

Using these embeddings, the theoretical measure of the rate of "information" generation by a system is the Kolmogorov-Sinai entropy(Grassberger, Schrieber et al. 1991). However this measure diverges to a value of infinity when the signal is contaminated by the slightest noise! A practical solution to these problems has been put forward using a family of statistics called the ApEn (Pincus, Gladstone et al. 1991), and SampEn (Richman and Moorman 2000). The ApEn, as applied to EEG signals in patients under general anesthesia, has been very well described in detail in an article by Bruhn(Bruhn, Ropcke et al. 2000). In short the ApEn looks at sequences of length m, and then establishes the negative logarithmic probability that these sequences predict a new sequence of $m+1$ points to within an error range of 'r' – typically set at 0.2×SD. In a regular signal most sequences will successfully predict the next data points, and the ApEn will be low. In an irregular signal, there will be few successful predictions and the ApEn will be correspondingly high. The exact value of the ApEn will depend on the values chosen for the three parameters of the statistic: N = number of samples, m = embedding dimension, and r = noise threshold. Bruhn suggested that for a data length of N = 1024 points, r = 0.2×SD, and m = 2; the maximum value of the ApEn should be about 1.7. Almost all published papers use low values of m = 2 or 3 in the calculation of the ApEn(Rezek and Roberts 1998). Because the ApEn(m=2) statistic is effectively only

extrapolating using a couple of previous data points, it may be merely applying a linear prediction. This may not be using any information beyond that more easily obtained from the SEN. In this paper we compared the ApEn obtained using values of m = 2 with those when using m = 5 and m = 10.

It is also possible to calculate an ApEn to estimate the similarity of two different signals - this is, confusingly sometime called the 'cross-entropy'. It should not be confused with the true Kullback-Liebler cross-entropy.

An alternative method for extracting information from the embedded time series data is to do a Singular-Value Decomposition (Broomhead DS and King GP 1986; Grassberger, Schrieber et al. 1991).

It is possible to decompose a matrix **U** into three matrices:

$$\mathbf{U} = \mathbf{C\Sigma V^T}$$

The 'singular values' are the positive square roots of the eigenvalues of a matrix (**C**) multiplied by its transpose ($\mathbf{V^T}$). The 'm' diagonal elements of the diagonal matrix **Σ** are the 'singular values'. Thus they can be thought of as 'pseudo-eigenvalues' of non-square matrices.

In our EEG embeddings (m=4, lag=2) the matrix (**U**) consists of 640×4 elements. Each of the 4 column vectors is the EEG signal lagged by 2×1000/sampling frequency (msec). If each column vector is independent of each other, then each singular value will be large. This is the case in the awake state, where we will have as many significant singular values as there are vectors. When the patient becomes anesthetized the EEG time series vectors become less independent - because the EEG develops slow oscillations (long-term temporal correlations). Thus the vectors that make up the matrix (**U**) are more dependent, and there a fewer significant singular values.

The Singular-value Decomposition Entropy (SVDen) was defined by Sabatini (Sabatini 2000) using the Shannon formula applied to the elements of **Σ** as follows:

$SVDen = -\Sigma\sigma_i \, ln \, \sigma_i$, where is normalized as $\sigma_i = \sigma_i / \mathbf{\Sigma}\sigma_j$ are the diagonal elements.

In essence, similar to the Spectral Entropy, the SDVen measure estimates the deviation of the singular values away from a uniform distribution.

EXPERIMENTAL COMPARISON OF ENTROPY ESTIMATORS

Methods.

Calculation of Entropies

The various entropy estimators were calculated according to standard algorithms (Inouye, Shinosaki et al. 1991; Fell, Roschke et al. 1996; Bruhn, Ropcke et al. 2000; Heneghan C 2000; Quiroga, Arnhold et al. 2000; Sabatini 2000). The SEN, GSE, and K-L were calculated over the frequency band 1 to 47Hz. The baseline for the K-L entropy was obtained from the single 5sec epoch of EEG data at the start of recording. A picture of how the entropy estimators transform the power spectral densities for a typical EEG epoch is shown in figure 1. We have plotted the transformed entropy value at each frequency (*k*) (ie. at the step before summing across the frequencies to produce the final entropy estimator). In the left upper graph we can see that the SEN_k is very close to the raw spectral density at each frequency bin in the awake (flat) spectrum. In contrast the right upper graph shows the peaked distribution characteristic of an anesthetized patient's EEG. The $p \times log(p)$ transformation has the effect of exaggerating the 'spectral density' around the spectral peaks. Conversely the reciprocal GSE transformation has the effect of increasing the 'spectral density' in the troughs of the spectrum.

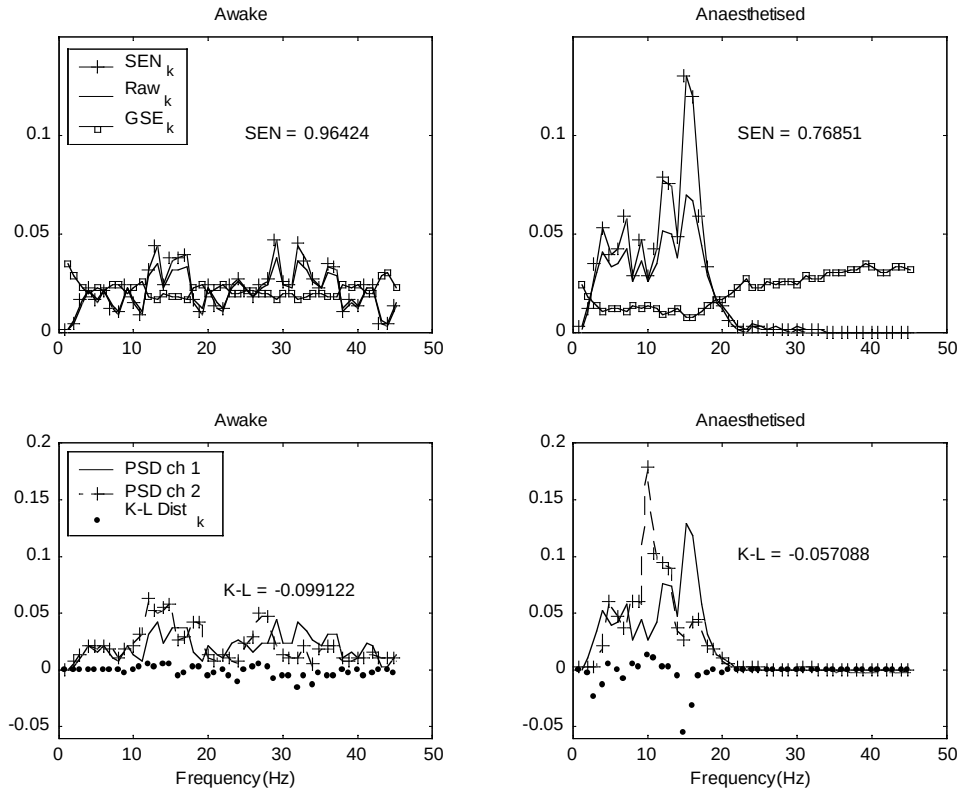

Figure 1. The effect of the entropy transformations in the frequency domain.

Examples of the values of different spectral entropy for each frequency bin. The horizontal axis of frequency(Hz), and vertical axis is spectral power. In this graph, the labels "RAW_k", "SEN_k", "GSE_k" and "$K\text{-}L_k$" refer to the values calculated for each frequency bin before summation. In the rest of the text the labels SEN, GSE and K-L refer to the totals of all the frequencies (*k*). The values of the GSE have been scaled to fit them on the same graph. The top row illustrate how the SEN

transformation exaggerates the peaks, and how the reciprocal (GSE) transformation smoothes the dips. The graphs in the bottom row are illustrative of the types of effects seen when using the K-L entropy. For graphical clarity we have compared the K-L between 2 contemporaneous EEG channels - not as in the text where we have compared the EEG spectrum at time (t) vs that at the start of the recording (t=5sec). They demonstrate pictorially the fact that negative distances are possible, and that the effective distance may be increased if the absolute value of the denominator is near zero.

For the ApEn we used $r = 0.2 \times SD$, $n = 1280$, lag = 2 data points, $m = 2$, 5 and 10. In the initial calculations of the SVDen it became apparent that the use of embedding dimensions greater than four did not contribute significant additional information, so a value of $m = 4$ was used for all calculations reported in this paper.

The detrended fluctuation analysis (DFA) is an efficient robust method of calculating the Hurst exponent of the data. In essence the signal is integrated and divided into epochs. Each epoch is detrended and the root mean square of the resultant fluctuations in each epoch obtained. As the size of the epochs increase, the root mean square of the fluctuations increase. If these increase in a linear bilogarithmic fashion, the slope of the line is the Hurst exponent (DFA). We calculated the slope using epochs ranging from 2 to 25 data points (~10 to 128Hz).

(A) Patients

After obtaining regional ethical committee approval and written informed consent, EEG data were obtained from 60 adult patients during induction of anaesthesia with propofol (1-2.5 mg/kg iv). Some of this data have been previously reported. The exact time at which the patients became unconscious (defined as becoming unresponsive to verbal command) was noted. The EEG signal was obtained from a bifrontal montage (F7: F8), via the Aspect A-1000 EEG monitor (Aspect Medical Systems, Newton, MA), using a sampling frequency of 256/sec, band-width1:47Hz, and 5sec epochs. The raw EEG data were then downloaded to a computer for offline analysis. The various entropy estimators were calculated from EEG data at the start (START = before induction of anaesthesia), 15sec prior to the point of loss-of-consciousness (LOC-15) , the point of loss-of-consciousness (LOC), 15sec after the point of loss-of-consciousness(LOC+15), and 30sec after the point of loss-of-consciousness(LOC+30). The exact epoch chosen for the 'start' epoch varied slightly because the exact epochs were selected manually as those containing minimal eye-blink and frontalis EMG artifact. There was no smoothing of any of the parameters.

(B) The AR2 model

This model was used because it generates series with known characteristics/oscillations, and it provides a 'test-bed' to compare the performance of the entropy estimators in a simple well-described system, without complication of unknown effects of non-linearities in the signal. Historically, higher order autoregressive models have been used to model the real EEG(Wright, Kydd et al. 1990). Data epochs of 1280 samples length were generated. The parameters of the AR2 model were chosen to give spectra similar to those encountered with real EEG's in patients undergoing general anesthesia (see figure 2).

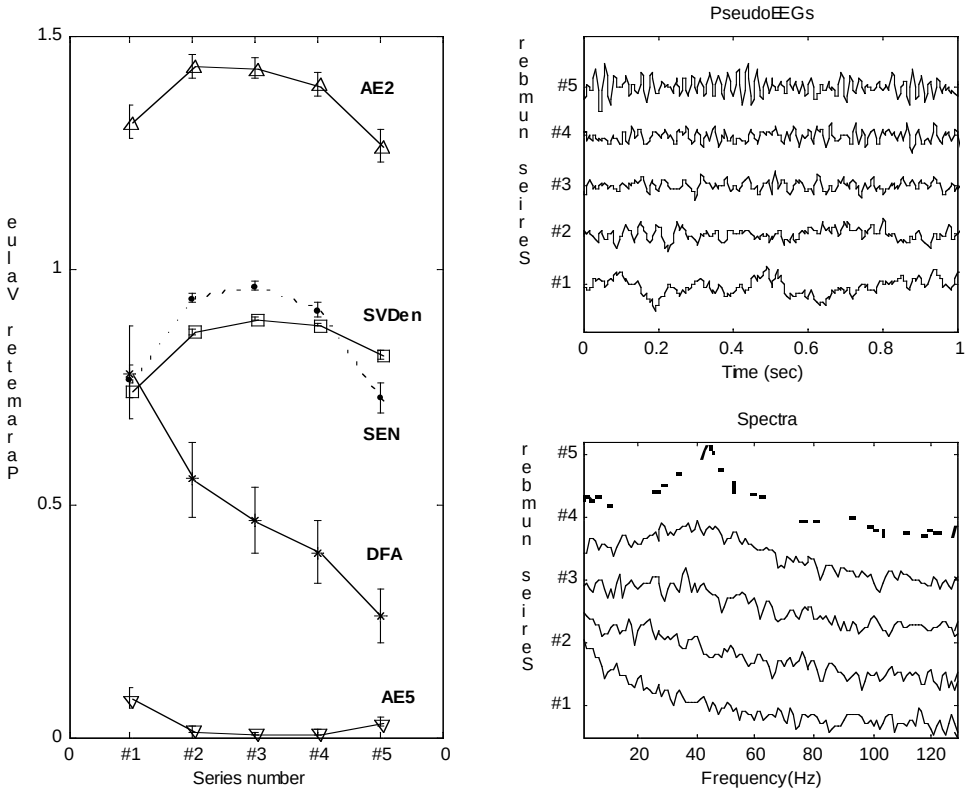

Figure 2. The AR2 model data. Time series, power spectra and accompanying changes in entropy estimators.

The $\rho 2$ value for series #1 to #5 were -0.09 to -0.99 in steps of 0.2. $\rho 2$ was kept constant at 0.99. The parameter values are expressed as the mean (± one SD) of 300 series. SEN=spectral entropy, DFA=detrended fluctuation analysis, SVDen=singular value decomposition entropy, AE2=approximate entropy (m=2), and AE5=approximate entropy (m=5). See text for details of the calculation of these parameters.

(C) Addition of Artifacts to White noise 'pseudoEEG's.

We created Gaussian white noise series (1280 samples length, equivalent to 5sec of real EEG data (Fs=256/sec), mean=0, SD=1) to simulate the EEG in the alert (pre-induction) state. We then added:

(i) low frequency (0.8Hz) sine wave oscillations to simulate eye movements

(ii) a step change half-way through the signal

(iii) a step change followed by an exponential return to the baseline

These produce waveforms similar to those seen with real blink artifacts (see figure 5). We progressively increased the magnitude of the artifact component of the signal from 1 to 6 units. We then calculated the various entropy estimators at each level of artifact magnitude, in order to evaluate how robust each estimator is to non-EEG noise.

(D) Added oscillations to patient data.

Because it is clear that the values of the various entropy estimators may be reduced by spectral peaks, we tested the effects of adding an artificial sine-wave to the patient EEG data set to produce a set of composite data (termed 'EEG+oscillations'). We added a computer-generated sine wave at three different frequencies (6.4Hz, 19Hz, and 32Hz). The amplitude was calculated such that the standard deviation (SD) of the sine-wave equalled the SD of the raw EEG signal. We trialled a number of different magnitudes and found that the effects on the entropy estimators were almost linearly related to the relative magnitude. Therefore we decided on the value of the SD because it appeared to produce a physiologically realistic magnitude of artifactual signal, but still showed an appreciable effect on the EEG parameter. Examples of the raw waveforms and the composite (EEG+oscillations) waveforms and spectral densities are shown in figure 3. Note that the y axis of the power spectra is a logarithmic scale.

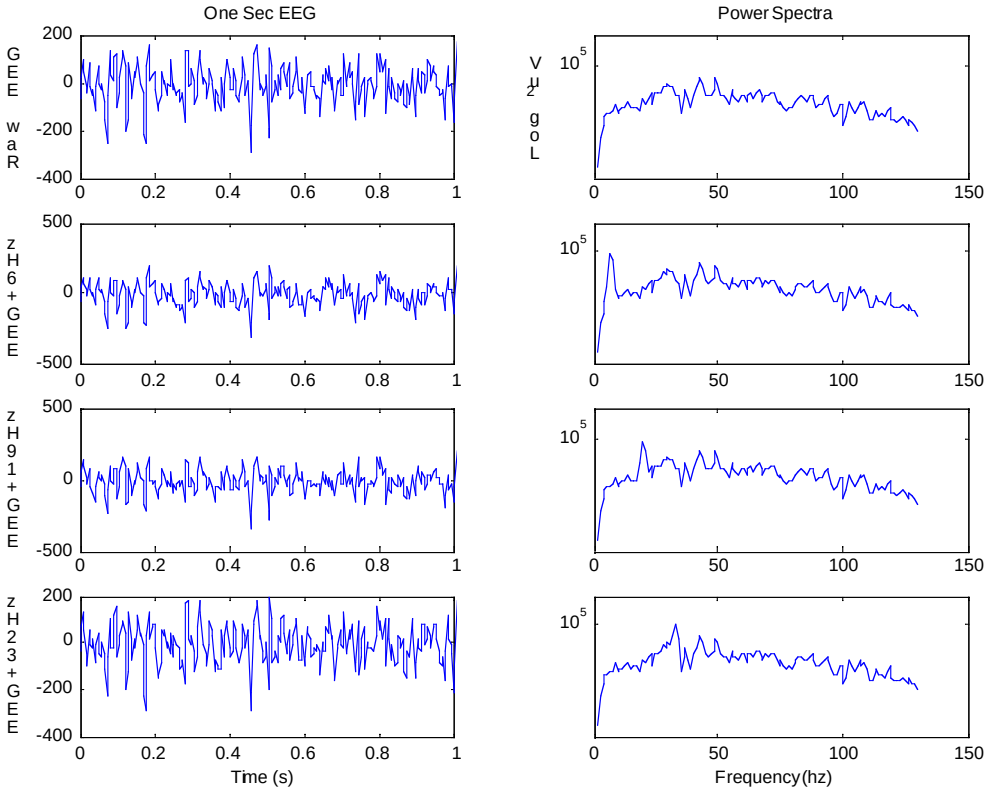

Figure 3a. Examples of the effects of added oscillations to EEGs of a patient while awake.

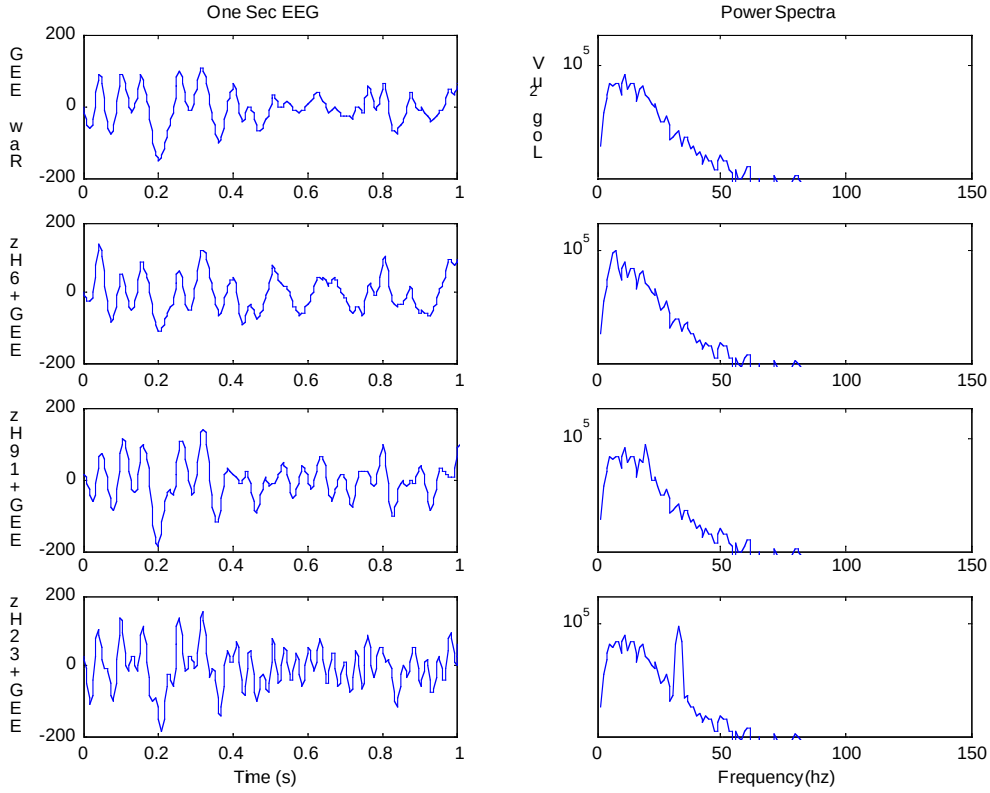

Figure 3b. Examples of the effects of added oscillations to EEGs of a patient while asleep.

Statistical Analysis

The relative efficacy of each parameter was compared using the area under the receiver operating curve (ROC) - using the values obtained at the START epoch (= awake state) with those obtained 30 sec after loss of consciousness (LOC+30) (= unconscious state). The ROC of each entropy estimator was compared pair-wise using a t-test.

Results.

(A) The Patient Data.

The changes in the different EEG parameters during induction were similar (table 1); and were comparable in differentiating the awake(START) from anaesthetised (LOC+30 sec) states. Interestingly ApEn(m=5, and m=10) increased significantly during induction of anesthesia. This is an opposite direction to that of ApEn(m=2).

Table 1. The changes in EEG entropy estimators (mean(SD)) at different points during induction of general anesthesia in the group of 60 patients.

(LOC = point of loss-of-consciousness – defined as no response to verbal command. ROC = area under receiver operating characteristic curve for awake(START) vs LOC+30sec time points.)

	Time				
Parameter	Start	LOC-15sec	LOC	LOC+30sec	ROC
DFA	0.63(0.22)	0.81(0.26)	1.11(0.21)	1.24(0.19)	0.97
SEN	0.90(0.06)	0.89(0.07)	0.82(0.07)	0.76(0.07)	0.93
GSE	0.90(0.05)	0.87(0.04)	0.81(0.08)	0.74(0.04)	0.95
SENhos	1.32(0.15)	1.26(0.14)	1.21(0.19)	1.12(0.16)	0.83
K-L	0.08(0.04)	0.13(0.14)	0.23(0.16)	0.29(0.17)	0.88
ApEn (m=2)	1.56(0.21)	1.53(0.18)	1.35(0.23)	1.18(0.28)	0.89
ApEn (m=5)	0.29(0.16)	0.35(0.17)	0.49(0.17)	0.57(0.28)	0.83
ApEn (m=10)	0.009(0.03)	0.003(0.01)	0.014(0.03)	0.03(0.05)	0.83
SVDen	0.98(0.02)	0.92(0.08)	0.82(0.10)	0.74(0.11)	0.97

All parameters changed significantly with time ($p<0.05$, paired t-test). The changes in each parameter were broadly comparable. There were no significant differences in the ROC curves for the different parameters except that ApEn (m=5, and m=10), and SENhos were less than the DFA and SVDen ($p<0.05$, t-test).

The Pearson linear correlation coefficients (*R*) between the different parameters for the combined patient data at all time points are shown in table 2. (Because ApEn(m=10) was very similar to ApEn(m=5) we have not included it for simplicity in presentation.)

Table 2. A matrix of the correlations between each parameter. (Measured using the Pearson linear correlation coefficient (*R*).)

	SEN	GSE	ApEn(m=2)	ApEn(m=5)	K-L	DFA(>10Hz)
SEN	1.00					
GSE	0.73	1.00				
ApEn (m=2)	0.61	0.61	1.00			
ApEn (m=5)	-0.53	-0.51	-0.91	1.00		
K-L	-0.23	-0.17	-0.16	0.13	1.00	
DFA	-0.69	-0.59	-0.64	0.56	-0.19	1.00
SVDen	0.68	0.73	0.78	-0.65	-0.27	-0.89

(B) Effects of oscillations on entropy measures
The AR2 simulated EEGs (see fig 2) show that both oscillatory spectral peaks (series #5), and a shift to low frequencies (series #1) reduce the SEN, GSE, and ApEn similarly compared to the pseudo 'awake' spectrum (series #3). In this linear, Gaussian, data set, the SEN is highly correlated with ApEn (r=0.91) and GSE (r=0.97).

(C) The effect of other 'simulated artifact' signals on the entropy estimators
Figure 4 shows how increasing the magnitude of the added artifact progressively reduces the entropy estimators from their value of one for pure white noise, (or 1.5 for the ApEn). In this simulation the embedding estimators seem to be more robust to the effects of noise than the spectral estimators. It can be seen that the effects on SEN are greater than those on GSE which in turn are less than SVDen and ApEn. The exception is the step-change where the estimators are similarly affected.

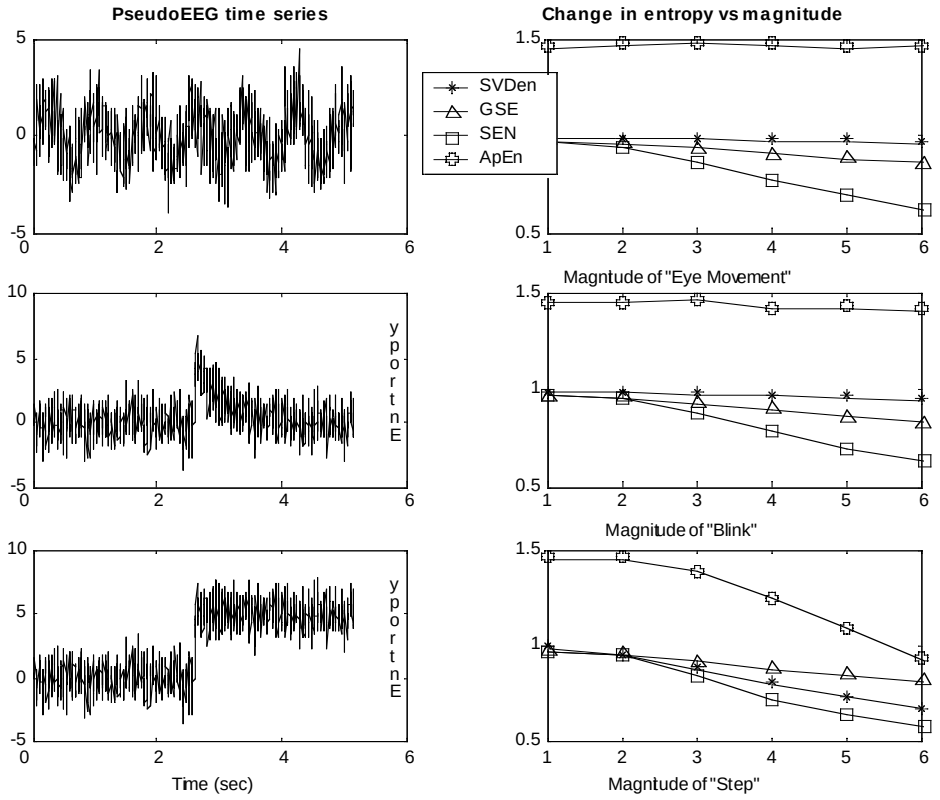

Figure 5. The effect of adding - (a) a low frequency (0.8Hz) sine wave, (b) a step and exponential decrease, and (c) a step - to a white noise 'pseudoEEG' signal. On the left are examples of the raw time series (with maximum amplitude added artifact). On the right are graphs showing how the values of the various entropy estimators are progressively reduced as the amplitude of the added artifact increases relative to the original white noise signal.

(D) The effect of added oscillations to real patient EEG data

Figure 6 is an example of the changes caused by adding artificial oscillations to real EEG data in one patient during induction of anesthesia.

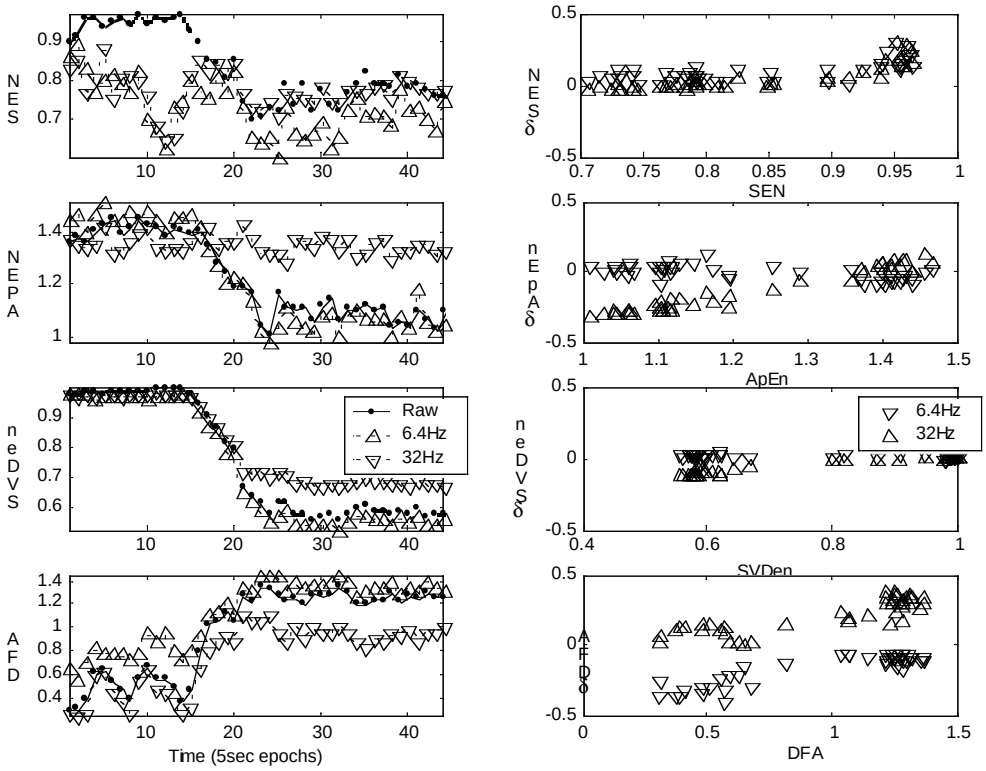

Figure 6. An example of the changes in entropy estimators during induction of anesthesia in patient #18 (raw). The effects of addition to the raw EEG of artificial oscillations at 6.4Hz(upward triangles) and 32Hz(downward triangles) on each entropy parameter are shown in the entropy estimator time-series' on the left. The plots on the right show oscillation-induced difference in each parameter (as indicated by the delta symbol) vs the actual value of the parameter as applied to the raw EEG data set. ApEn = approximate entropy(m=2), SEN = spectral entropy, SVDen = entropy of the singular value decomposition(m=4), and DFA = detrended fluctuation analysis.

A typical example of the effects of the oscillation on the major entropy estimators is shown in figure 6. It suggests that the SEN, when the patient is awake, is least robust to the oscillation - as compared to the ApEn and the SVDen. Also it is apparent that the oscillations have differing influence depending on whether the patient is awake (high SEN >0.75) or comatose (corresponding to a low SEN<0.75). The oscillations tend to decrease the SEN when the patient is awake, but have less effect when the patient is comatose. Also the effects are relatively insensitive to the frequency of the imposed oscillation. In contrast, when the patient is awake, the ApEn and SVDen are relatively insensitive to added oscillations. However both these measures are artificially increased maximally if the patient is comatose and the frequency is above 30Hz (figure 5 and table 3). The SEN is less affected, and even further decreased in the unconscious patient. The DFA is resistant to the effects of oscillation in both the awake and unconscious states.

Table 3. Combined data from all patients.

	Coefficient of variation (R^2)					
Time	Start (Awake)			30sec post loss-of-consciousness		
Frequency of added Oscillation (Hz)	6.4	19	32	6.4	19	32
SEN	0.24	0.09	0.08	0.75	0.78	0.82
ApEn	0.88	0.91	0.76	0.94	0.86	0.86
SVDen	0.96	0.96	0.94	0.99	0.97	0.93
DFA	0.85	0.84	0.80	0.97	0.72	0.64

The degree of agreement between the raw EEG and the 'oscillation+EEG' data was quantified using the coefficient of variation (R^2). Clearly, the SEN in the awake patients was most sensitive to the addition of exogenous oscillatory activity, when compared to the other measures.

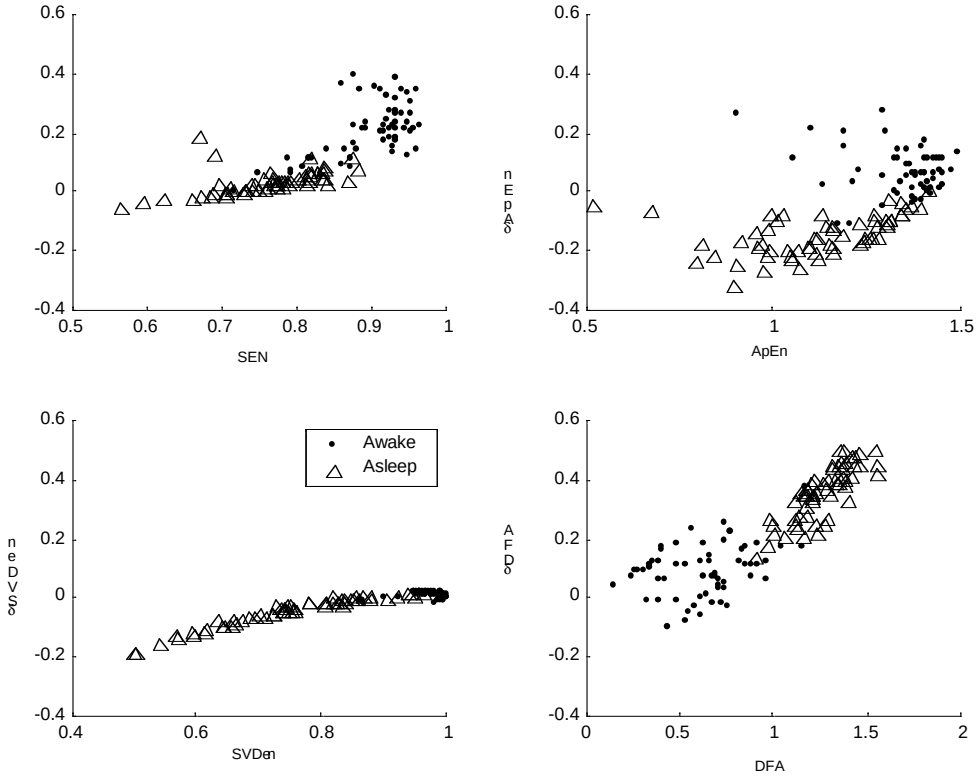

Figure 7. Difference between raw EEG and EEG+32Hz (delta) vs actual raw EEG values. Data are combined from all 60 patients. (Awake=START, and asleep=LOC+30sec epochs.)

The slope of all curves is positive This indicates that the addition of 32Hz oscillations tends to decrease the values (the delta is positive) of each parameter when these parameters have high values, and increase the parameter values (delta is negative) when the parameters take on low values. The absolute differences are least for the SVDen. The approximately linear nature of the curves (with the possible exception of the ApEn) suggests that the effect of added oscillations is not constant but highly dependent on the properties of the pre-existing EEG signal.

Discussion.

Although the different entropy estimators were closely correlated with each other when applied to the AR2 model data, they were less well inter-correlated when compared using real EEG data. It was difficult to establish whether the differences between the different entropy estimators were due to inherent differences in the type of information that they obtained from the EEG signal, or whether the differences could be merely attributed to different degrees of numerical robustness of the signal processing and algorithms.

Theoretically both ApEn and SEN measure the dynamic changes of the EEG. The SEN measures in the frequency domain, and the ApEn in the time domain (phase-space, or alternatively, Markov-space). The ApEn and SEN produced very similar results from AR2-generated pseudoEEG data. This suggests that the two entropy estimators are probably equivalent when applied to data derived from a linear system - both achieving maximal values with uncorrelated white noise, and decreasing when the signal becomes more correlated.

When analyzing the real EEG data, it seemed that embedding-derived entropy estimators (ApEn and SVDen) were less affected by the addition of exogenous oscillations than spectrum-derived entropy estimators (SEN, GSE, K-L). The reason why this should be so is not entirely clear. Intuitively, even a high-frequency sine-wave oscillation (32Hz) should be extremely regular, and therefore the addition of such a wave to the (irregular) raw waveform in from an awake patient should have the effect of making the signal more regular on average, and lowering the ApEn in all cases. We observed that when patients were anesthetized, the addition of such an oscillation had the opposite effect – elevating the ApEn in a frequency dependent manner. This may be explained as the addition of the high frequency oscillation to a signal with an existing large low-frequency peak, it has the effect of making the spectrum flatter and broader (see fig 3b). Hence the increased ApEn. This is evidence that, in practice, ApEn does not purely estimate ‘regularity’ as has been claimed(Pincus, Gladstone et al. 1991), but actually estimates the effective narrowness of the EEG power spectrum. Most patients receiving modest doses of midazolam or propofol will exhibit a pronounced spectral peak in the beta frequency-band. Our data would predict that the effect of this phenomenon on the various entropy estimators will therefore differ (either elevate or depress the estimator); depending on whether there is existing background of delta activity in the EEG. The same argument could be applied to the effect of spindles (transient 10-14Hz EEG oscillations), on the values of the various entropy estimators.

The SEN and GSE quantify the degree to which the EEG spectrum deviates from white noise (marked by a uniformly distributed spectrum). During increasing depth of anesthesia (with GABAergic agents), the EEG spectrum develops an increasingly steeper slope (the DFA jumps from ~0.5 to ~1.5), and the SEN and GSE decrease from their maximal values of one. The K-L entropy measures the 'distance' that the spectrum lies from a reference spectrum. In our case the spectrum was obtained from the awake patient just prior to the start of induction of anesthesia. Because the EEG spectrum in the awake (and nervous) patient is often comparable to the uniform white-noise spectrum, the K-L entropy of the spectrum uses much the same information as the SEN. All spectral-derived measures are relatively sensitive to artifacts such as frontalis EMG and eye-blinks and eye-movements - which cause episodic enormous increases in low frequency power. It must be noted that the 'deleterious' effects on the SEN, caused by adding oscillations to the true EEG, may have been less if we had used more aggressive pre-processing and filtering of the EEG data to reduce the effect of artifacts. Our data represents 'worst-case', real-life data taken during busy surgical lists. This most closely resembles the day-to-day use of EEG monitoring in anesthesia.

The approximate entropy is derived in a substantially different fashion – being a practical approximation to the true Kolmogorov-Sinai entropy. With m = infinity, and r = 0, the ApEn = Kolmogorov-Sinai entropy. It is said to estimate the inherent predictability of the signal. However, crucially, its properties will depend on the dimension of the embedding space (m). It is a recurring problem in using nonlinear techniques to quantify the EEG, that there is not sufficient stationary data to enable to reliable high dimensional embedding. In our calculation of ApEn, m = 2 implies that we are using the previous EEG data point (since we used lag of 2 data points (= 1/128sec), about 8msec) to predict the next data point. The irregularity measure will therefore be 'predicting' the data point 8msec into the future – thus, effectively the general anesthetic-induced decrease in ApEn(m=2) is an estimate of the loss of high frequencies. With m = 10 the ApEn is using information from data sequences up to ~100msec into the past. Therefore the ApEn(m=10) is weighted towards the influence of lower frequencies. Presumably this is the explanation as to why ApEn(m=10) increases with increasing depth of anesthesia - compared with ApEn(m=2) which decreases. In simple terms, the ApEn(m=2) estimates the anesthetic-induced decrease in gamma waves, whereas the ApEn(m=10) estimates the anesthetic-induced increase in theta and delta waves. This opposite direction of change for ApEn(m=5 or 10) vs ApEn(m=2) was also seen using the linear AR2 model data. This would imply that this paradoxical phenomenon is caused by intrinsic properties of the ApEn algorithm, and is not due to non-linearities in the EEG signal.

This study shows that induction of general anaesthesia with propofol causes similar changes in magnitude in all EEG entropy estimators, mediated predominantly by a decrease in relative high frequency components of the EEG signal. Furthermore a decrease in the value of the entropy estimator of the EEG does not differentiate between either the appearance of an oscillation, or an increase in slope of the spectrum. Conversely, the addition of a high-frequency oscillation on top of an already steeply sloped spectrum, causes a paradoxical increase in ApEn and SVDen, but less predictable

changes in the SEN and DFA. The ApEn(m=2) changes in an opposite direction to that in the ApEn(m=5) or ApEn(m=10) in transitions between consciousness and unconsciousness. These data are not in contradiction to the hypothesis that the effect of GABAergic general anesthesia causes the EEG (and hence cortical function) to become simpler relative to the conscious state.

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