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Sample Entropy Tracks Changes in EEG Power Spectrum With Sleep State and Aging

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Abstract

The regularity of EEG signals was compared between middle-aged (47.2 ± 2.0 yrs) and elderly (78.4 ± 3.8 yrs) female subjects in Wake (W), NREM stages 2 and 3 (S2, S3), and REM. Signals from C3A2 leads of healthy normal subjects, acquired from polysomnograms obtained from the Sleep Heart Health Study, were analyzed using both Sample Entropy (SaEn) and power spectral analysis (delta, theta, alpha, and beta frequency band powers). SaEn changed systematically and significantly ($p < 0.001$) with sleep state in both age groups, following the relationships $W > REM > S2 > S3$. SaEn was found to be negatively correlated with delta power and positively correlated with beta power. Small changes in SaEn appear to reflect changes in spectral content rather than changes in regularity of the signal. A better predictor of SaEn than the frequency band powers was the logarithm of the power ratio $(\alpha + \beta) / (\delta + \theta)$. Thus, SaEn appears to reflect the balance between sleep-promoting and alertness-promoting mechanisms. SaEn of the elderly was larger than that of middle-aged subjects in S2 ($p = 0.029$) and REM ($p = 0.001$), suggesting that cortical state is shifted towards alertness in elderly subjects in these sleep states compared to middle-aged.

Keywords

elderly; polysomnography

A. Introduction

Aging is associated with major changes in the quality and structure of sleep. Sleep efficiency is reduced in older subjects and the percent of time spent in restorative slow wave sleep (SWS) decreases markedly [Dijk, et al., 2001]. The incidence of sleep fragmentation and the frequency of arousals and awakenings also increase significantly with age [Boselli, et al., 1998; Klernan, et al., 2004; Bonnet and Arand, 2007]. Analyses of EEG signals document these changes but have provided limited insight regarding the neurophysiological mechanisms underlying them. Although there are shifts in the power spectrum of the EEG with increasing age in both wakefulness and sleep, the mechanisms responsible for these changes and their relationship to changes in the quality and structure of sleep are poorly understood [Dustman et al., 1985; Giaquinto and Nofre, 1986; Dijk et al., 1989; Veldhuizen et al., 1993; Larson et al., 1995; Mourtazaev et al., 1995; Shigeta et al., 1995; Carrier et al., 2001; Feinberg and Campbell, 2003; Mann and Roschke, 2004]. On the one hand, such changes may reflect age-related alterations in functional connections among cortical and subcortical neuronal networks that determine sleep state or in the functional and physical properties of these neural circuits. On the other hand, such differences may represent alterations in modulating inputs to brainstem

or thalamocortical circuits related to extrinsic factors such as the greater incidence of sleep-disordered breathing and of joint pain in elderly subjects.

To further probe the EEG for aging-related differences that might not be apparent from the power spectrum, various measures which reflect the temporal “regularity” of a signal have been investigated [Roschke et al. 1993; Roschke et al. 1995; Anokhin et al. 1996; Fell et al. 1996; Pereda et al. 1998; Pezard et al. 1998; Burioka et al. 2001; Burioka et al. 2003; Shen et al. 2003; Terry et al. 2004; Abasolo et al. 2005; Acharya et al. 2005]. Several such measures are based on the concept of entropy. Approximate Entropy (ApEn) and related measures of “irregularity” have been shown to have their highest values in W and REM, and to decrease progressively with deepening of sleep in NREM (but only significantly so in SWS) [Fell et al. 1996; Acharya et al. 2005]. These findings are qualitatively consistent with the visual observation that the EEG is most regular in SWS, when it is dominated by large-amplitude delta waves, and less regular in waking (W) and REM, when there are many high frequency components present. ApEn, and the similar measure Sample Entropy (SaEn), of EEG signals have also been shown to differ in some leads between normal subjects and Alzheimer's Disease patients [Abasolo, et al., 2005; Abasolo, et al., 2006].

Interpreting such findings with respect to neurophysiological mechanisms, however, is difficult because these measures do not have unique relationships to the properties of the underlying neural circuits [Acherman et al. 1994; Theiler and Rapp 1996; Burioka et al. 2003; Shen et al. 2003; Jeong, 2004; Abasolo et al. 2006]. The questions of how to relate complexity of physiological data to heterogeneity at the cellular level, and whether or not increased irregularity implies increased physiological complexity, have been raised previously (e. g., see commentaries on complexity in aging and disease which are discussed by Vaillancourt and Newell [2002]). These issues are still controversial. Furthermore, even the usual interpretation that an increase in entropy implies a “more irregular” signal may not be strictly true when applied to a computer-sampled (i. e., digitized) signal. This issue is important because calculations of power and entropy are based on sampled signals. Consider, for example, the calculation of ApEn of a true sine wave having a frequency f_0 . ApEn is based on the negative logarithm of the probability of having sequences of 2 (or 3) data points occur repeatedly throughout a time series [Pincus, 1991]. If the sampling (or digitizing) frequency is much higher than f_0 , then many samples will be acquired within each cycle of the sine wave and each cycle will be well represented by the sampled data points. In this case, pairs (or triplets) of data points from one cycle are likely to be similar to pairs (or triplets) of data points from other cycles, and the calculated probabilities will be much closer to one than to zero; thus, calculated ApEn will be small (because $\log(1) = 0$). But as the sampling frequency decreases, there will be less repetition of sampled data points from cycle to cycle and the probability of matches will decrease; thus, calculated ApEn will increase. Therefore, the apparent “regularity” of a digitized signal can differ from the actual regularity of the corresponding undigitized signal; consequently, interpretations of ApEn, and the related index SaEn, in terms of “regularity” of EEG signals are potentially misleading.

A digitized EEG signal contains components at frequencies much lower than the sampling frequency as well as at higher frequencies. On the basis of the preceding discussion, one may expect that the components at low frequencies will cause calculated entropy to tend towards zero, whereas those at higher frequencies will increase its value. Therefore, we expect that calculated entropy will reflect the relative amounts of the high-frequency (entropy-raising) and low-frequency (entropy-lowering) components. In this study we hypothesized that: (i) changes of entropy of EEG signals with sleep state will be closely correlated with the relative amounts of high-frequency and low-frequency powers, and; (ii) entropy of EEG signals during sleep will be higher in the elderly because of the known shift towards more high-frequency and less low-frequency power in EEGs from these subjects [Dijk, *et al.*, 1989; Ehlers and Kupfer,

1989; Veldhuisen, *et al.*, 1993; Larson, *et al.*, 1995; Carrier, *et al.*, 2001; Darchia, *et al.*, 2007]. To test these hypotheses, we analyzed SaEn of EEG signals from female human subjects during wakefulness and in NREM and REM sleep in two age groups, middle-aged (42–50 yrs) and elderly (71–86 yrs). Across all of these data we observed a linear relationship between SaEn and the logarithm of the ratio of high-frequency to low-frequency power of the EEG signal. To further establish the basis of this relationship, we also analyzed simulated EEG signals and found that a similar relationship of entropy to power levels was valid. This relationship suggests that SaEn measures the major changes in balance of high-frequency and low-frequency powers in the EEG signal with sleep state, which correlate with visual impressions of regularity. Smaller changes in this balance with aging or disease are detected by SaEn; however, these latter changes may be explained by known differences in EEG power spectra and may be unrelated to “regularity”, *per se*.

B. Methods

1. Subjects

Sample entropy analyses were conducted on previously-existing overnight polysomnogram (PSG) EEG datasets obtained from the NIH-sponsored Sleep Heart Health Study (SHHS) [Quan *et al.* 1997]. We selected from the SHHS database 20 middle-aged and 20 elderly Caucasian women who did not have sleep-disordered breathing or a history of stroke and were not taking any medications known to interfere with sleep. The mean age of the middle-aged women was 47.2 ± 2.0 yrs (range: 42–50 yrs), and the mean age of the elderly women was 78.4 ± 3.8 (range: 71–86 yrs). The body mass indices for these women were <30 . None of the women in the study were current smokers. Apnea-hypopnea index (AHI) for these subjects was 1.48 ± 2.48 in the middle-aged subjects and 2.54 ± 2.54 in the elderly.

2. Nocturnal Polysomnography

The overnight PSG studies were conducted in the SHHS participants' homes by certified technicians [Redline *et al.*, 2004]. The PSG data recorded for each subject included: EEGs recorded from leads C3A2 and C4A1, a right and a left electro-oculogram (EOG), a bipolar submental electromyogram (EMG), electrocardiogram (EKG), nasal airflow, respiratory excursions of the thorax and abdomen, and finger pulse oximetry. Sleep staging was scored by SHHS personnel at 30s intervals based on the Rechtschaffen and Kales (R&K) criteria [Rechtschaffen and Kales 1968]. SHHS personnel had previously marked apneas, hypopneas, and arousals on the PSGs. We initially identified segments of EEG signals that were heavily contaminated by EOG by visually comparing the C3A2 and C4A1 EEGs with the left and right EOG signals.

Cerebral montage C3A2 was used for the EEG analyses. For each subject, we attempted to select six 30s segments of simultaneous EEG and EOG recordings from each of the states (Wake, Stage-2 (S-2), Stage-3 (S-3), and REM) during the first NREM-REM episode of the night; however, in a few instances only 4 or 5 segments were selected because signal quality was visually unacceptable (often due to strong contamination from EOG signals). We avoided selecting data during, or within 15 sec of, an apnea, hypopnea, or arousal. Wake data were acquired before the subject fell asleep. All data during sleep were taken between the onset of the first NREM 2 episode and the end of the first REM episode. For the middle-aged subjects, the mean numbers of 30s segments analyzed per subject in each sleep stage were as follows: Wake = 5.8; S-2 = 6.0; S-3 = 5.7; and REM = 5.6. For the elderly subjects, the mean numbers of 30s segments analyzed per subject were: Wake = 5.9; S-2 = 6.0; S-3 = 6.0; and REM = 5.4. The total number of 30s segments analyzed was 925.

3. Signal Analysis

In the SHHS PSGs, EEG signals were sampled at 125 Hz and EOG signals at 50 Hz. Each EEG signal to be analyzed was first upsampled to 250 Hz, then downsampled to 50 Hz. Both the (downsampled) EEG and the EOG signal were lowpass filtered at 25 Hz using a 20th-order finite-impulse-response filter based on a Hamming window. Corresponding 30s segments of the EOG and (downsampled) EEG signals were wavelet decomposed using Daubechies wavelet of order 4 (MATLAB Wavelet Toolbox). The EEG and EOG components below 3 Hz were extracted as the approximation signals (EOGF, EEGF) at the appropriate decomposition level. An optimal noise-removal FIR filter was designed using a minimum mean-square error criterion [Clarkson, 1993]. Using EOGF as input to the designed filter, the output of the filter is the optimal estimate of the signal components of EEGF that are linearly correlated with EOGF. This output was then subtracted from EEGF to obtain the EOG-free EEGF approximation signal. The order of the filter was chosen by testing different filter lengths until two criteria were satisfied: (i) the impulse response declined to, and stayed near, zero in <1 sec, and (ii) the coherence between the filtered EEGF signal and the EOGF signal at frequencies below 3 Hz was <0.2. Finally, the filtered EEGF signal was added to the EEG wavelet detail components above 3 Hz to form the (30 sec) signal for SaEn calculation.

Conceptually, Sample Entropy is based on the conditional probability that two sequences of length “m+1” randomly selected from a signal will “match”, given that they match for the first “m” elements of the sequences. Here “match” means that the distance between the sequences is less than some criterion “r”. Distance is measured in a vector sense. The conditional probability is estimated as the ratio of the unconditional probabilities of the sequences matching for lengths “m+1” and “m”, and SaEn is calculated as the negative logarithm of this conditional probability [Richman and Moorman, 2000]. Thus, SaEn is defined as

$$\text{SaEn} (m, r, N) = - \ln [A^m(r) / B^m(r)]$$

where, $B^m(r)$ is the estimated probability that two sequences match for m points, and $A^m(r)$ is the estimated probability that the sequences match for m+1 points. $A^m(r)$ and $B^m(r)$ are evaluated from data using a relative frequency approach. SaEn was calculated using m = 2 and r = 20% of the standard deviation of the 30s data sequence. Defining r as a fraction of the standard deviation eliminates the dependence of SaEn on signal amplitude.

For 16 subjects (8 from each age group) power of the EEG signal was calculated in different frequency bands, defined as very low frequency (VLF) region (0–0.5 Hz), delta region (0.67 – 3.83 Hz), theta region (4.0 – 7.83 Hz), alpha region (8.0 – 11.83 Hz) and beta region (12.0 – 20.0 Hz). The spectral density was estimated (Matlab signal processing toolbox) for every 30 sec record using Welch's method (nine 6-sec subsegments with 50% overlap of consecutive subsegments). Power in a frequency band was calculated as the product of the frequency resolution and the sum of the spectral densities in the band. Relative power in each frequency band is the ratio of power in the respective band to the sum of the powers in all bands.

4. Statistical Analyses

We determined the mean (+/- S. D.) SaEn value for Wake and three sleep stages. Differences ($P < 0.05$) between SaEn values for sleep stage (Wake, Stage 2, Stage 3 and REM) and age (middle-aged women vs. elderly women) were assessed by a two factor analysis of variance (ANOVA) followed by a Tukey post-hoc test (SYSTAT 9).

A two-factor ANOVA was also used to determine the significance of the effects of age and sleep stage on each relative power (alpha, beta, delta, and theta) and the effects of the interaction

between age and sleep stage on EEG power. The Tukey post-hoc test was used to correct for multiple comparisons.

Multiple linear regression analysis of SaEn on relative alpha, beta, delta and theta power was conducted to determine which of these variables was a significant predictor of SaEn.

5. Generation of synthetic EEG signals

A set of 500 simulated EEG-like signals having various levels of power in the delta (0.5–3.9 Hz), theta (4.1–7.9 Hz), alpha (8.1–11.9 Hz), and beta (12.1–20.0 Hz) bands were generated in MATLAB™. In each case a Gaussian white noise sequence was filtered by 4 bandpass elliptic filters, one for each of the delta, theta, alpha, and beta bands. To create a simulated EEG signal, the 4 filter outputs were added with weights that were selected so that the ranges of relative powers of the 500 simulated signals covered those observed in the actual EEG recordings. The weights were determined by random selections from uniform distributions. In addition, 5 sets of 200 simulated signals each were generated in a similar fashion except that the same weights were used for all 200 signals in a set. Analyses of these latter data sets provided estimates of the reproducibility of SaEn in signals having the same theoretical power levels.

C. Results

1. Distribution of Sample Entropy Values in Wake, S-2, S-3, and REM: (Figure 1)

Histograms showing the distribution of SaEn values obtained for all of the 30-sec EEG segments analyzed in each sleep stage in the 20 middle-aged and the 20 elderly subjects are presented in Figure 1. There was relatively little overlap between the range of SaEn values in Wake and in S-2 for both the middle-aged and the elderly subjects. The overlap between S-2 and S-3 was somewhat greater than that between Wake and S-2, and the extent of overlap was greater in the middle-aged than in the elderly subjects. For both age groups the overlap was quite small between S-3 and REM, but somewhat greater overlap was observed between Wake and REM, especially in the elderly subjects.

In a representative example of 30-sec SaEn values obtained over a 34 min period of S-2 ($n = 23$) and a 24 min period of REM ($n = 15$), SaEn values were relatively consistent within each of the two sleep stages (Figure 2). In addition, there was no evidence of a systematic upward or a downward trend as each of the sleep stages progressed.

2. Changes in Sample Entropy (SaEn) with Sleep Stage: (Table 1)

Mean SaEn values for each age group during each sleep stage are presented in Table I. In both the 20 middle-aged and the 20 elderly subjects, SaEn values decreased significantly from Wake to S-2 ($p < 0.0001$), and from S-2 to S-3 ($p < 0.0001$). REM SaEn values were significantly greater than SaEn in S-2 ($p < 0.0001$) and in S-3 ($p < 0.0001$), but less than SaEn during Wake ($p < 0.0001$) in both age groups. These data may be compared to SaEn values previously reported [Mathew, *et al*, 2006] for EEG signals from 8 young (22.5 $\pm$ 4.9 yrs) females. SaEn in Wake from these young subjects (1.85 $\pm$ 0.14) was similar to that of the two older groups, but SaEn in S-2 (1.29 $\pm$ 0.17), S-3 (1.05 $\pm$ 0.27) and REM (1.34 $\pm$ 0.17) is noticeably smaller in the young subjects.

The differences between mean SaEn values for Wake vs. S-2, S-2 vs. S-3, S-3 vs. REM, and Wake vs. REM, were determined for each of the 20 middle-aged and the 20 elderly subjects. The sign of the change of SaEn when sleep state changed was highly consistent across subjects and within subjects. For each subject in both age groups, the mean Wake SaEn value was greater than the mean SaEn value for S-2. In addition, S-2 SaEn values were also greater than

S-3 values for each subject in both age groups and mean SaEn values in REM were uniformly greater than S-3 SaEn values. The signs of mean differences between Wake and REM were not quite as consistent as the differences between other sleep stages. However, the mean SaEn value for Wake was greater than the REM value in all 20 middle-aged subjects and was statistically greater in the elderly subjects ($18 +, 2 -$; $p < 0.001$, Wilcoxon sign test).

3. Influence of Age on Sample Entropy Values: (Figure 3)

Although Wake SaEn values were essentially the same in the middle-aged (1.985 ± 0.125) and the elderly subjects (1.977 ± 0.130), S-2 SaEn values were significantly higher in the elderly women (1.652 ± 0.108) than in the middle-aged women (1.601 ± 0.120) ($p < 0.029$). In contrast, SaEn during S-3 did not differ significantly between the two age groups. However, the difference between the age groups was highly significant during REM ($p = 0.001$) where SaEn values were higher for the elderly women (1.842 ± 0.094) than for the middle-aged women (1.772 ± 0.103).

4. Power Spectral Density in Middle-Aged and Elderly Subjects: (Figure 4)

ANOVA of the power spectra of 30-sec EEG segments (on which SaEn values had previously been determined) was conducted for randomly-selected subsets of 8 of the 20 middle-aged and 8 of the 20 elderly subjects. Mean values for relative delta power were higher in the middle-aged subjects than in the elderly in all sleep stages: Wake ($p = 0.001$); S-2 ($p < 0.0001$); S-3 ($p = 0.026$); REM ($p < 0.0001$). (Figure 4) Relative beta power was significantly higher in elderly than in middle-aged subjects in Wake ($p < 0.0001$), and in REM ($p = 0.004$). Alpha power was higher in elderly than in middle-aged subjects during S-2 ($p = 0.045$) and REM ($p = 0.006$), but the differences between the age groups were not significant during Wake and S-3.

We then performed a multiple linear regression analysis of SaEn on relative alpha, beta, theta, and delta band powers across both age groups (16 subjects) and all sleep stages. An F-test on these pooled data indicated significance of the regression ($p < 0.0001$). Because the regression coefficient between alpha power and SaEn was non-significant, the alpha power was removed and the regression analysis was recalculated. The linear regression of SaEn on relative beta, theta, and delta power indicated significant positive regression coefficients between SaEn and beta power (slope = 1.592) ($p < 0.0001$) and between SaEn and theta power (slope = 0.270) ($p < 0.006$) and a significant negative coefficient between SaEn and delta power (slope = -0.693) ($p < 0.0001$). When the multiple regression was performed separately for the two age groups, SaEn was correlated only with delta and beta powers for the middle-aged group, but was dependent on delta, theta, and beta powers for the elderly.

Predicted SaEn values calculated from this regression equation were compared to the actual SaEn values of these data records (Figure 5). Approximately 75% of the data points in the middle range fell in the vicinity of the line of identity whereas the highest and lowest SaEn values fell to the left of the line, e.g., predicted values were greater than actual values. (Figure 5) In the mid-range of the plot, the SaEn values for elderly subjects tended to fall to the right of the line of identity, e.g., the actual values were slightly higher than the predicted values.

5. Relation of SaEn to high and low frequency powers (Figure 6)

SaEn from actual EEG signals exhibited a linear relationship to the natural log of the ratio of (alpha+beta) power to (delta+theta) power. The slight deviation from linearity at high power ratios reflects waking situations in which high-frequency power was greater than low-frequency power (Figure 6). Overall, this linear prediction of SaEn showed less systematic error than did the prediction based on multiple linear regression of SaEn versus individual powers (Figure 5). To explore the differences of SaEn between the two age groups, SaEn was

plotted vs. the logarithmic power ratio for S2 and REM separately (Figure 7). There does not appear to be any systematic difference in this relationship between the age groups.

6. Analysis of simulated EEG signals

Five hundred simulated EEG signals, having various power levels in the delta, theta, alpha, and beta ranges, were analyzed using the same algorithms that were applied to the actual EEG signals (Figure 8). The weighting factors used to add together the outputs of the 4 bandpass filters were chosen to achieve the range of relative powers observed in the actual EEG signals (Figure 4). The slope and intercept of a linear fit to these data were similar to those for the corresponding data from actual EEG signals (slope: 0.221 vs. 0.243; intercept: 2.067 vs. 1.977). Curvilinearity at high power ratio is more evident in the simulated data, and a quadratic fit was evaluated in order to compare the actual and simulated data. When compared to Figure 6, the quadratic fit to SaEn of the simulated data is somewhat higher (~0.15) than SaEn of the actual EEGs over much of the range of the log power ratio.

A multiple linear regression of SaEn of simulated EEGs against the 4 relative power levels was performed. The resulting regression coefficient was similar to that found for the actual EEG signals for delta power (−0.653 vs. −0.693); the coefficients differed from those for actual EEGs for theta (−0.440 vs. 0.270) and beta powers (0.883 vs. 1.592).

Even for the simulated EEGs there is considerable scatter about the regression fits. To estimate the statistical variability in calculating the log power ratio and SaEn from single time series that all have the same properties, we generated 5 sets of 200 simulated signals each, using the same summation weights for all 200 signals of a set (Figure 9). The logarithmic power ratios were nearly the same for every signal in a set and SaEn exhibited small variability within each set that was noticeably less than that seen for the actual or simulated EEG analyses of Figures 6 and 8.

D. Discussion

In this study we found that Sample Entropy of an EEG signal changes with sleep state in middle-aged and elderly subjects and this variation with sleep state was highly consistent in each subject in both age groups. Furthermore, SaEn was significantly larger in elderly than middle-aged subjects in sleep stages 2 and REM, and SaEn in these age groups was larger during sleep than SaEn reported for younger female subjects. We also found that the relative powers in the EEG bands differed between the middle-aged and elderly subjects. Delta power was higher in middle-aged subjects in all sleep states, whereas alpha and/or beta powers were higher in elderly subjects in W, Stage 2, and REM (Figure 4). These latter findings are consistent with previous reports [Larsen et al. 1995; Carrier et al. 2001].

Numerous studies have attempted to correlate indices of the regularity of an EEG signal with sleep state. Correlation dimension, largest Lyapunov exponent, Approximate Entropy, and Sample Entropy have all been found to be larger in W, NREM 1, and REM than in NREM 3/4. Occasionally an index was reported to differ between sleep stages 2 and 3/4. Although the trend is suggested by earlier studies, this study is the first to demonstrate that one such index, SaEn, differs significantly among W, NREM 2, NREM 3, and REM. We initially attempted to evaluate SaEn in NREM 1, but this sleep stage was not included because of the technical difficulty of identifying enough acceptable episodes of NREM 1 in the elderly subjects. We did not attempt to analyze NREM 4 in addition to NREM 3 because NREM 4 is often absent in the elderly. One may speculate that for the middle-aged subjects SaEn in NREM 4 would be less than it is in NREM 3 because of the further increase in delta power. It should be noted that we restricted our analyses to the first NREM-REM cycle of the night. It is unclear whether SaEn during subsequent NREM-REM cycles would be quantitatively the same as we observed;

however, because delta power decreases systematically during the night whereas beta or sigma activity may increase [Tagoya et al., 2000; Carrier et al., 2001; Perlis et al., 2001; Roschke and Mann, 2002; Darchia et al., 2007], SaEn in a given sleep state may increase with each new cycle.

SaEn is an indicator of the extent to which a signal which has similar values in two different time windows will continue to have similar values as the size of the window over which the comparison is made increases. Small SaEn implies that the values continue to be similar. Thus, it is natural to consider SaEn as an indicator of how reproducible the signal is at different times, which may be considered a marker of regularity. Lyapunov exponents also compare a signal at two different times for which the values are similar. These exponents indicate how rapidly the values will become dissimilar as time progresses. Thus, a periodic signal (which is highly regular) has a Lyapunov exponent equal to zero. Correlation dimension is based on measuring the number of points in a signal whose values fall within a small neighborhood of a given point. Correlation dimension represents the rate of change of this number of points as the neighborhood size changes. For a highly irregular signal, the points are distributed randomly and the number of points increases directly with the volume of the neighborhood; thus, its correlation dimension is large. All three measures, therefore, can be related to the concept of regularity of a signal; however, an important question is whether there are alternative explanations for a change in one of these measures. We argued in the Introduction that the digitizing frequency is a complicating factor in interpreting changes in SaEn, and our findings support the hypothesis that SaEn values may reflect the interplay of low and high frequency signal components on the calculation of SaEn rather than changes in the inherent regularity of the signal.

The dependence of SaEn on sleep state may be an expression of the changing regularity of the EEG as observed visually, which has been reported for the EEG of Alzheimer's Disease patients in Wake [Abasolo et al., 2005, 2006]. On the other hand, the analyses of simulated EEG signals suggest that a significant fraction of the changes in SaEn are related to the effect of the distribution of power versus frequency. For both actual and simulated EEG signals, delta and beta powers are predictors of SaEn in the qualitative directions proposed earlier. That is, SaEn decreases as low-frequency (i. e., delta) power increases and SaEn increases as high-frequency (i. e., beta) power increases. Power at intermediate frequencies either did not correlate significantly with SaEn (i. e., alpha power) or was not uniformly significant (i. e., theta power). When analyzed by age group, theta power was a predictor of SaEn only for the elderly group, but this dependence on theta power was present also when the data were pooled into one group.

The other finding which supports our hypothesis is the nearly linear relationship between SaEn and $\log(\alpha + \beta) / (\delta + \theta)$. This relationship, valid for both actual and simulated EEGs, exhibited some curvilinearity at high relative power ratios at which high-frequency power exceeds low-frequency power. It seems likely that the SaEn calculation saturated at these levels of high-frequency power because these values are similar to those determined for Gaussian white-noise signals. In retrospect, given the result that alpha (and sometimes theta) powers were not significant linear predictors of SaEn, use of $\log(\beta / \delta)$ may have been sufficient as a predictor of SaEn. It should be remembered that we have used relative powers in these calculations rather than absolute powers. Despite the trends, there is significant scatter in the graphs of Figures 6 and 8. Figure 9 indicates that repeated calculations on time series having the same theoretical properties produces less variability than seen in the actual or simulated data. For the actual EEG signals, one can surmise that the presence of transient signal features (e. g., spindles, K-complexes, delta bursts) contributes to this variability. For the simulated EEG signals, it is probable that the relative power levels which occurred (due to selecting random values of weighting coefficients) encompass broader ranges than seen in real EEG signals. Furthermore, this factor may underlie the fact that, on average, SaEn based on

simulated signals tends to be higher than that from real signals, especially when the logarithmic power ratio was below 0.

Other investigators have interpreted changes in EEG “regularity” with sleep state or disease as an indicator of changes in the complexity of neural connections and/or circuitry in the cortex. It has been suggested that higher entropy signifies that underlying neural dynamics are more complex [Jeong, 2001], that entropy reflects the extent of interactions between (cortical) areas [Pezard, 1998], and that reduced entropy implies “deficient information processing” [Abasolo, 2005]. Furthermore, other measures of irregularity, such as correlation dimension and auto mutual information, have been interpreted as indicators of the number of oscillating circuits generating the EEG [Anokhin, 1996] or as reflections of the loss of neurons or synapses [Jeong, et al., 2001]. However, it is highly questionable whether, on the basis of EEG measurements alone, it is possible to distinguish such effects from those due to altered inputs to cortical neurons. Furthermore, these studies did not recognize the potential effect of the distribution of power versus frequency on calculated entropies.

Our findings may be relevant to a proposed balance between a sleep-promoting mechanism and an alertness mechanism and how this balance changes with sleep state [Corsi-Cabrera et al., 2006]. The transition from Wake to NREM 1, and ultimately to NREM 2, involves a progressive increase in low-frequency (e. g., 2–8 Hz) power of the EEG and decrease of high-frequency (e. g., > 9 Hz) power [Corsi-Cabrera et al., 2000, 2006; Tanaka et al. 2000]. Across NREM-REM cycles, delta and beta powers change reciprocally [Roschke and Mann, 2002] and the transition from NREM 2 to REM is associated with a decrease in delta [Hadjiyannakis et al., 1997] although the delta power is still greater than, and the beta power less than, that observed in NREM 1 [Corsi-Cabrera et al., 2006]. The time courses of these changes differ between the low-frequency and high-frequency powers. As sleep deepens, delta power rises more slowly than beta power falls (although beta power may plateau after the first few minutes of NREM) [Tagoya et al., 2000; Ferrara et al., 2002]. In addition, the fluctuations of delta and beta powers are negatively correlated in NREM and positively correlated in REM [Roschke and Mann, 2002]. Although these findings exhibit some topographical variations, especially along the anteroposterior direction, collectively they are compatible with the hypothesis that delta power (or delta plus theta) represents a neurophysiological process which promotes sleep, while beta power (and perhaps higher frequencies) represents a process which promotes alertness or arousal [Uchida et al., 1994; Hadjiyannakis et al., 1997; Tanaka et al., 2000; Corsi-Cabrera et al., 2006]. We found SaEn to have an overall negative correlation with relative delta power and positive correlation with relative beta power. Thus, SaEn may primarily reflect the shifting balance between alertness-promoting and sleep-promoting mechanisms. That is, SaEn may be considered to be an integrative index of the net level of alertness.

Our ability to establish differences in SaEn with sleep state was facilitated by avoiding the potentially confounding effects of contamination by EOG signals. In the former regard, an optimal, least-squares, filter design was applied to each data record to estimate and remove any EEG signal component that was correlated with the ipsilateral EOG signal. To prevent the removal of EEG components that were coincidentally contained in the EOG recording, we used wavelet filtering to extract only the EOG signal components below 3 Hz for removal from the EEG. This procedure could possibly remove some EEG components in the delta range; however, the procedure for the filter design involved user evaluation of the filter based on such factors as the coherence between the filtered EEG signal and the EOG signal. (It should be close to zero.) Usually if there was significant bidirectional contamination between the EOG and EEG signals, an acceptable filter design could not be achieved (because of difficulties in matching the phase differences at different frequencies), and that data segment was discarded. Another potential concern is our use of a relatively low sampling frequency (50 Hz). This frequency was chosen because the original EOG signals were acquired with 50 Hz sampling

by SHHS. Thus, use of the SHHS data necessitated that we lowpass filter the EEG signal with a cutoff frequency of 25 Hz, possibly eliminating some signal components above that frequency. Power in the original signal was quite small above 20 Hz and it seems unlikely that loss of these components had a significant effect. In addition, our definition of the beta frequency band includes frequencies often designated as the sigma band that are associated, in particular, with sleep spindles. Since SaEn was strongly correlated with beta power in all sleep states (data not shown), and since spindles (a contributor to sigma power) are a significant feature of NREM 2 only, it seems likely that power in the sigma band was not the major contributor to the correlation of SaEn with beta power across all sleep states.

The distributions of SaEn values (Figure 1) show clear differences between sleep states in both age groups with, however, some overlap of the SaEn values in some but not all sleep states. The behavior of SaEn in individual subjects is not apparent from these histograms. Although the quantitative differences in SaEn between sleep states exhibited intersubject variability, the signs of these changes were very highly consistent. Only 2 of the 160 comparisons were inconsistent, and both were W-REM comparisons in elderly subjects. Thus, for the great majority of subjects SaEn was highly correlated with sleep state. It should be remembered, however, that the analyzed EEG segments were carefully selected to be free from artifacts and other transient events, and the SaEn values in a sleep state were averaged. The actual values and the variability of SaEn in each sleep state were subject dependent. Several recent studies have argued that sleep state is more finely graded than the Rechtschaffen and Kales stages represent, and they have proposed various measures of these gradations in sleep state [Kubicki and Herrmann, 1996; Himanen and Hasan, 2000; Kaplan et al., 2001]. SaEn might be useful as part of a battery of indices from which sleep state might be estimated. Even though our preliminary observations suggest that SaEn is reproducible throughout a sleep state (Figure 2), it seems likely that a closer examination may reveal systematic changes within a state because progressive changes in EEG power spectra have been described, especially near the beginning and end of a sleep stage [Tagoya et al., 2000; Ferrara et al., 2002; Roschke and Mann, 2002; Merica and Fortune, 2004]. Furthermore, it is possible to evaluate SaEn on shorter data records and thereby obtain a finer discrimination in time as well. On the other hand, SaEn is influenced by irregularly occurring events, such as K-complexes and spindles, and these events may cause unacceptable variability in SaEn if very short data records are used.

SaEn was found to be higher in elderly subjects in Stage 2 and REM. These differences were small (Figure 3), about half of the typical differences between sleep states in either age group. The graphs of SaEn vs. logarithmic power ratio for S2 and REM (Figure 9) suggest that this relationship is unchanged between the middle-aged and elderly subjects, and that SaEn is higher in the elderly because a larger fraction of the individual values occur at higher SaEn. Since SaEn during Wake in the elderly did not differ from that in middle-aged subjects, the higher values in Stage 2 and REM suggest a cortical state in the elderly that is nearer to the Wake state. One may speculate that the increased frequency of arousals from these two sleep states in the elderly may reflect, in part, a persistent predisposition towards a more “awake” cortical state. For example, SaEn might be elevated in the elderly if an increase in SaEn during an arousal persists for some time following termination of the arousal (even if R&K sleep state is unchanged).

In conclusion, we have demonstrated that Sample Entropy varies systematically with sleep state in healthy middle-aged and elderly female subjects. SaEn falls progressively with deepening of sleep from Wake to NREM 3 (and probably to NREM 4), then increases in REM to a value below that in Wake. Furthermore, this progression of values was highly consistent in individual subjects. In sleep stage 2 and REM, SaEn is larger in elderly subjects than in the middle-aged, perhaps reflecting an elevated propensity for cortical state in sleeping elderly to be nearer to the waking state. In middle-aged and elderly female subjects SaEn was

systematically higher in sleep than was previously reported for young females. SaEn was shown to be correlated with relative power in the delta, theta, and beta bands. SaEn appears to represent the balance between high frequencies (primarily beta power) and low frequencies (primarily delta power) in the EEG signal. Our findings cast doubt on the interpretation that changes in SaEn represent changes in regularity of EEG signals which can be related to the properties of cortical neural circuits. In particular, small changes in SaEn of EEG signals appear to reflect changes in spectral content rather than changes in regularity of the signal. However, SaEn can be interpreted as a measure of the balance between sleep-promoting and alertness-promoting neural mechanisms.

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Figure 1. Histograms of SaEn of all 925 30-sec EEG segments grouped by age and sleep state for 20 middle-aged and 20 elderly subjects.

Figure 2. Reproducibility of SaEn within a sleep state. SaEn was calculated for individual 30-sec records obtained during one Stage 2 episode and the subsequent REM episode. Female subject, age 76.

Figure 3.

Effects of age and sleep state on mean SaEn values in Wake, S-2, S-3, and REM. 20 middle-aged subjects: solid bars. 20 elderly subjects: open bars. * $p = 0.029$; ** $p = 0.001$.

Figure 4.

Influence of age on relative powers in the main frequency bands in each sleep state. Solid bars: 8 middle-aged subjects. Open bars: 8 elderly subjects. *p = 0.045; **p = 0.006; ***p < 0.001; ****p < 0.0001

Figure 5.

SaEn predicted from the multiple regression on relative frequency band powers for individual 30-sec data records from 8 middle-aged and 8 elderly subjects in all sleep stages vs. SaEn calculated for the corresponding data record. Line of identity is also shown.

Figure 6.

Calculated SaEn vs. the logarithm of the ratio of (alpha+beta) power to (delta+theta) power for 378 actual EEG recordings from 8 middle-aged and 8 elderly subjects. Each point represents one 30-sec data record. Dotted line is the linear regression fit: $y = 1.977 + 0.243 x$. Solid line is the polynomial regression fit: $y = 1.982 + 0.1596 x - 0.0435 x^2$.

Figure 7. SaEn vs. logarithmic power ratio for actual EEG recordings from sleep stages 2 (left) and REM (right). Open symbols: middle-aged subjects. Solid symbols: elderly subjects.

Figure 8.

Calculated SaEn vs. the logarithm of the ratio of (alpha+beta) power to (delta+theta) power for 500 simulated EEG recordings. Each point represents one 30-sec data record. Dotted line is the linear regression fit: $y = 2.067 + 0.221 x$. Solid curved line is the polynomial regression fit: $y = 2.0463 + 0.1527 x - 0.0226 x^2$.

Figure 9.

Calculated SaEn vs. the logarithm of the ratio of (alpha+beta) power to (delta+theta) power for 5 sets of 200 signals each. Each point represents one 30-sec data record.

Table 1

Sample Entropy of 20 middle-aged and 20 elderly women in various sleep states.

	WAKE	S-2	S-3	REM
Elderly	1.98+/-0.13 *	1.65+/-0.11 *	1.36+/-0.15 *	1.84+/-0.09 *
Middle Aged	1.99+/-0.12 **	1.60+/-0.12 **	1.39+/-0.14 **	1.77+/-0.10 **

* = significantly different than other sleep stages in the middle-aged group (p<0.0001)

** = significantly different than other sleep stages in the elderly group (p<0.0001)