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Entropy analysis of the EEG background activity in Alzheimer's disease patients

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder. Although a definite diagnosis is only possible by necropsy, a differential diagnosis with other types of dementia and with major depression should be attempted. The aim of this study was to analyse the electroencephalogram (EEG) background activity of AD patients to test the hypothesis that the regularity of the AD patients' EEG is higher than that of age-matched controls. We recorded the EEG from 19 scalp electrodes in 11 AD patients and 11 age-matched controls. Two different methods were used to estimate the regularity of the EEG background activity: spectral entropy (SpecEn) and sample entropy (SampEn). We did not find significant differences between AD patients and control subjects' EEGs with SpecEn. On the other hand, AD patients had significantly lower SampEn values than control subjects ($p < 0.01$) at electrodes P3, P4, O1 and O2. Our results show an increase of EEG regularity in AD patients. These findings suggest that nonlinear analysis of the EEG with SampEn could yield essential information and may contribute to increasing the insight into brain dysfunction in AD in ways which are not possible with more classical and conventional statistical methods.

Keywords: Alzheimer's disease, electroencephalogram, sample entropy, spectral entropy

1. Introduction

Alzheimer's disease (AD) is the most frequent cause of dementia, and is characterized by progressive impairments in cognition and memory whose course lasts several years prior to death (Jeong 2004). These clinical features are accompanied by characteristic histological changes in the brain, which include widespread cortical atrophy, intracellular deposition

of neurofibrillary tangles and extracellular deposition of senile plaques, particularly in the hippocampus and the cerebral cortex (Selkoe 1994). AD is considered to be the main cause of dementia in western countries (Bird 2001), and although a definite diagnosis is only possible by necropsy, a differential diagnosis with other types of dementia and with major depression should be attempted. Magnetic resonance imaging and computerized tomography can be normal in the early stages of AD, but a diffuse cortical atrophy is the main sign in brain scans. Mental status tests are also useful.

The electroencephalogram (EEG) has been used as a tool for diagnosing dementias for several decades. The hallmark of EEG abnormalities in AD patients is a shift of the power spectrum to lower frequencies and a decrease of coherence among cortical areas (Jeong 2004), although in the early stages of the disease the EEG may exhibit normal frequencies (Markand 1990). These abnormalities are thought to be associated with functional disconnections among cortical areas resulting from death of cortical neurons, axonal pathology, cholinergic deficits, etc (Jeong 2004).

Recent progress in the theory of nonlinear dynamics has provided new methods for the study of the EEG (Jeong 2004). Nonlinearity as a necessary condition for chaotic behaviour is present in many dynamical systems found in nature, including the brain. Nonlinearity in the brain is introduced even at the cellular level, since the dynamical behaviour of individual neurons is governed by threshold and saturation phenomena. Moreover, the hypothesis of an entirely stochastic brain can be rejected due to its ability to perform sophisticated cognitive tasks. Given the highly nonlinear nature of the neuronal interactions at multiple levels of spatial scales, the EEG appears to be an appropriate area for nonlinear time series analysis (Kantz and Schreiber 1997).

There are many studies in which nonlinear time series analysis techniques were applied to different kinds of EEGs. These investigations of the electrical activity of the brain have revealed possible medical applications, since analysis based on nonlinear dynamics yields information unavailable from traditional EEG spectral-band analysis (Pritchard *et al* 1994). Moreover, they have given rise to the possibility that the underlying mechanisms of the brain function may be explained by nonlinear dynamics (Babloyantz and Destexhe 1988, Röschke *et al* 1995, Stam *et al* 1995). Particularly, several studies have examined the nonlinear dynamics of the EEG in AD. It has been found that AD patients have lower correlation dimension (D_2) values—a measure of dimensional complexity of the underlying system (Grassberger and Procaccia 1983a)—than control subjects (Pritchard *et al* 1994, Stam *et al* 1995, Jeong *et al* 1998, 2001a). These results show a decrease in the complexity of the electrical activity in brains injured by AD (Jeong 2004). The first Lyapunov exponent ($L1$) has also been used to characterize nonlinear behaviour (Wolf *et al* 1985). It has been shown that AD patients have significantly lower $L1$ values than controls in almost all EEG channels (Jeong *et al* 1998, 2001a). However, the amount of data required for meaningful results in the computation of D_2 and $L1$ is beyond the experimental possibilities for physiological data (Eckmann and Ruelle 1992). Moreover, the Grassberger and Procaccia algorithm or its modifications used to estimate D_2 assume the time series to be stationary (Grassberger and Procaccia 1983b), something generally not true with biological data. Therefore, it becomes necessary to study the EEG background activity with different methods. For instance, mutual information analysis (Jeong *et al* 2001b) and synchronization likelihood (Stam *et al* 2003, Pijnenburg *et al* 2004) have been used to assess information transmission between different cortical areas in AD.

One possible alternative solution lies in computing the entropy of the EEG. Entropy is a concept addressing randomness and predictability, with greater entropy often associated with more randomness and less system order. Recently, a number of different estimators have been introduced to quantify the entropy of time series. These approaches may be loosely

classified into two groups: spectral entropies and embedding entropies (Sleigh *et al* 2004). Spectral entropies estimate the changes in the amplitude component of the power spectrum of the EEG, using the amplitude components at each frequency of the power spectrum as the probabilities in the entropy calculations (Sleigh *et al* 2004). On the other hand, embedding entropies provide information about how the EEG signal fluctuates with time by comparing the time series with a delayed version of itself (Sleigh *et al* 2004).

The present study was undertaken to examine the EEG background activity in AD with two different entropy definitions: spectral entropy (SpecEn) and sample entropy (SampEn). SpecEn is the Shannon entropy formula suitably normalized and applied to the power spectral density of the EEG signal (Sleigh *et al* 2004), while SampEn is an embedding entropy that quantifies the irregularity (or complexity) in data without the drawbacks that widely used nonlinear methods (D_2 and $L1$) have (Richman and Moorman 2000). We wanted to test the hypothesis that the entropy of the AD patients' EEG would be different from that of age-matched controls, hence indicating an abnormal type of dynamics in this group.

The paper is organized as follows. In section 2, we explain the selection of patients and controls, the EEG recording and how artefact-free epochs were chosen. SampEn and SpecEn are also introduced in section 2, as well as the statistical tools used to evaluate the differences between entropy values for AD patients and control subjects. Section 3 presents the results of our study. Finally, in section 4 we discuss our results and compare them with other studies of the EEG background activity in AD patients with nonlinear analysis methods, and we draw our conclusions.

2. Materials and methods

2.1. Subjects and signals

Twenty-two subjects participated in this study. Eleven patients (five men and six women; age = 72.5 ± 8.3 years, mean ± standard deviation (SD)) fulfilling the criteria of probable AD were recruited from the Alzheimer's Patients' Relatives Association of Valladolid (AFAVA) and referred to the University Hospital of Valladolid (Spain), where the EEG was recorded. All of them had undergone a thorough clinical evaluation that included clinical history, physical and neurological examinations, brain scans and a Mini-Mental State Examination (MMSE), generally accepted as a quick and simple way to evaluate cognitive function (Folstein *et al* 1975). The mean MMSE score for the patients was 13.1 ± 5.9 (mean ± SD), with five of them having a score of less than 12 points, indicating a severe degree of dementia. Two patients were receiving lorapezam. With therapeutic doses, benzodiapzepines may enhance beta activity, although no prominent rapid rhythms were observed in the visual examination of their EEGs. None of the other patients used medication that could be expected to influence the EEG.

The control group consisted of 11 age-matched, elderly control subjects without past or present neurological disorders (seven men and four women; age = 72.8 ± 6.1 years, mean ± SD). The MMSE score value for all control subjects was 30.

The local ethics committee approved the study. All control subjects and all caregivers of the demented patients gave their informed consent for participation in the current study.

2.2. EEG recording

EEGs were recorded from the 19 scalp loci of the international 10–20 system (electrodes Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz and Pz, all of them

being referenced to the chin). More than 5 min of data were recorded from each subject using a Profile Study Room 2.3.411 EEG equipment (Oxford instruments). Sample frequency was 256 Hz, with a 12-bit A-to-D precision. Recordings were made with the subjects in a relaxed state and under the eyes-closed condition in order to obtain as many artefact-free EEG data as possible.

All EEGs were visually inspected by a specialist physician to check for eye movement and other artefacts. Thus, only EEG data free from electro-oculographic and movement artefacts, and with minimal electromyographic (EMG) activity were selected for the entropy computations. Afterwards, EEGs were organized in 5 s artefact-free epochs (1280 points) that were copied as ASCII files for off-line analysis on a personal computer. An average number of 30.0 $\pm$ 12.5 artefact-free epochs (mean $\pm$ SD) were selected from each electrode for each subject. Furthermore, all recordings were digitally filtered with a band-pass filter with cut-off frequencies at 0.5 Hz and at 40 Hz in order to remove EMG activity prior to the SampEn and SpecEn calculations.

2.3. Spectral entropy (SpecEn)

Shannon defined the information concept of entropy as the expected value (i.e. the average amount) of the information of a probability distribution (Shannon 1948). Shannon's definition of entropy has been applied, modified and proven valid in a variety of fields. In 1979, Powell and Percival introduced spectral entropy (SpecEn), based on the peaks of the Fourier transform, as a measure of regularity (Powell and Percival 1979). This definition was also extended to the relative power spectral density of the EEG by Inouye *et al* (1991) and can be calculated with the following expression:

$$H(f) = -\frac{1}{\ln(N)} \sum_{i=1}^{N} p_i \ln(p_i), \tag{1}$$

where p_i are the spectral amplitudes of frequency bin i (assuming a bin width of one spectral unit), the sum of all p_i is equal to 1 and N is the number of frequency bins (Sleigh *et al* 2004). The p_i can be obtained as the normalized value of the power spectral density at each frequency bin (Rezek and Roberts 1998).

SpecEn is a convenient way of quantifying the distribution of spectral power, as it measures the flatness of frequency spectrum. A high SpecEn implies a flat, uniform spectrum with a broad spectral content, whereas a low SpecEn implies a spectrum with all the power condensed into a single frequency bin (i.e. a less complex, more predictable signal) (Sleigh *et al* 2004). This entropy estimator has been applied to measure the irregularity of the EEG during rest and mental arithmetic tasks, with results showing that EEGs during rest were significantly more irregular anteriorly than in the occipital areas (Inouye *et al* 1991). Fell *et al* (1996) have shown that SpecEn is a useful discriminator of sleep stages, as its value decreases significantly from stage II to stages III and IV. Moreover, the use of SpecEn to study epilepsy shows promise. The background EEG is disorganized in or near the epileptogenic focus and focal background abnormalities can therefore be estimated by SpecEn (Inouye *et al* 1992). It has been demonstrated that this entropy measure is useful in the extraction of features from EEG recordings of a patient during Cheyne–Stokes respiration (Rezek and Roberts 1998). Furthermore, SpecEn has been used to monitor the depth of anaesthesia (Rezek and Roberts 1998, Zhang and Roy 2001), and the algorithm has even been implemented in the Datex-Ohmeda S/5^{TM} Entropy module (Viertiö-Oja *et al* 2004). SpecEn can be used to detect subtle changes in the EEG background activity. It has been shown that it decreases abruptly as the

patient becomes unconscious during induction of general anaesthesia, and does not decrease significantly with further deepening of the anaesthesia (Sleigh *et al* 2004).

In this pilot study, we estimated the SpecEn of the EEG background activity of AD patients and control subjects with a short computer program, developed with MATLAB®. The spectral power density was obtained as the Fourier transform of the autocorrelation function of the EEG signals. The different p_i were obtained as the normalized value of the power spectral density, with respect to the total spectral power in the 0.5 to 40 Hz band, at each frequency. We wanted to test if this method could be useful for the detection of the differences in the power spectrum between both groups, as one of typical abnormalities in AD is a shift of the power spectrum to lower frequencies.

2.4. Sample entropy (SampEn)

As we have previously mentioned, embedding entropies provide information about how the EEG signal fluctuates with time by comparing the time series with a delayed version of itself (Sleigh *et al* 2004). Several embedding-based formulae have been proposed in an attempt to estimate the Kolmogorov–Sinai (KS) entropy with reasonable precision, such as K_2 entropy (Grassberger and Procaccia 1983c) or the Eckmann and Ruelle entropy (Eckmann and Ruelle 1985). However, these methods to estimate the entropy of a system represented by a time series are usually not well suited to short and noisy data sets, such as biomedical signals. To overcome this drawback, Pincus introduced a family of statistics named approximate entropy (ApEn) (Pincus 1991). ApEn provides a widely applicable, statistically valid formula that will distinguish data sets by a measure of regularity (Pincus 1991).

ApEn examines time series for similar epochs and assigns a non-negative number to the sequence, with larger values corresponding to more complexity or irregularity in the data (Pincus 1991). Briefly, given N points, ApEn(m, r, N) measures the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same tolerance width r) on subsequent incremental comparisons. The ApEn algorithm counts each sequence as matching itself to avoid the occurrence of ln(0) in the calculations and this has led to discussion of the bias of ApEn (Richman and Moorman 2000).

To reduce this bias, Richman and Moorman have developed and characterized a new family of statistics: SampEn (Richman and Moorman 2000). Two input parameters, a run length m and a tolerance window r, must be specified to compute SampEn. SampEn(m, r, N) is the negative logarithm of the conditional probability that two sequences similar for m points remain similar at the next point, where self-matches are not included in calculating the probability. Thus, a lower value of SampEn also indicates more self-similarity in the time series. SampEn is largely independent of record length and displays relative consistency under circumstances where ApEn does not (Richman and Moorman 2000). In addition to eliminating self-matches, the SampEn algorithm is simpler than the ApEn algorithm, requiring one-half as much time to calculate.

Formally, given N data points from a time series $\{x(n)\} = x(1), x(2), \ldots, x(N)$, to define SampEn, one should follow these steps:

1. Form m vectors $X_m(1), \ldots, X_m(N - m + 1)$ defined by $X_m(i) = [x(i), x(i + 1), \ldots, x(i + m - 1)]$, for $1 \leqslant i \leqslant N - m + 1$. These vectors represent m consecutive x values, commencing with the ith point.
2. Define the distance between vectors $X_m(i)$ and $X_m(j)$, $d[X_m(i), X_m(j)]$, as the maximum absolute difference between their scalar components:

$$d[X_m(i), X_m(j)] = \max_{k=0,\ldots,m-1}(|x(i + k) - x(j + k)|). \tag{2}$$

3. For a given $X_m(i)$, count the number of j ($1 \leqslant j \leqslant N-m$, $j \neq i$), denoted as B_i, such that the distance between $X_m(i)$ and $X_m(j)$ is less than or equal to r. Then, for $1 \leqslant i \leqslant N-m$,

$$B_i^m(r) = \frac{1}{N-m-1} B_i. \tag{3}$$

4. Define $B^m(r)$ as

$$B^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} B_i^m(r). \tag{4}$$

5. We increase the dimension to $m+1$ and calculate A_i as the number of $X_{m+1}(i)$ within r of $X_{m+1}(j)$, where j ranges from 1 to $N-m$ ($j \neq i$). We then define $A_i^m(r)$ as

$$A_i^m(r) = \frac{1}{N-m-1} A_i. \tag{5}$$

6. We set $A^m(r)$ as

$$A^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} A_i^m(r). \tag{6}$$

Thus, $B^m(r)$ is the probability that two sequences will match for m points, whereas $A^m(r)$ is the probability that two sequences will match for $m+1$ points.

We define sample entropy by

$$\text{SampEn}(m, r) = \lim_{N \to \infty} \left\{ -\ln \left[\frac{A^m(r)}{B^m(r)} \right] \right\}, \tag{7}$$

which is estimated by the statistic

$$\text{SampEn}(m, r, N) = -\ln \left[\frac{A^m(r)}{B^m(r)} \right]. \tag{8}$$

It is imperative to consider SampEn(m, r, N) as a family of parameters: comparisons are intended with fixed m, r and N. N is the length of the time series, m is the length of the sequences to be compared and r is the tolerance for accepting matches. It is convenient to set the tolerance as r times the standard deviation of the original data sequence. This gives SampEn scale invariance, in that it remains unchanged under uniform process magnification, reduction or constant shift to higher or lower values (Pincus 1991, Richman and Moorman 2000).

Although m and r are critical in determining the outcome of SampEn, no guidelines exist for optimizing their values. In principle, the accuracy and confidence of the entropy estimate improve as the number of matches of length m and $m+1$ increases. The number of matches can be increased by choosing small m (short templates) and large r (wide tolerance) (Lake *et al* 2002). However, there are penalties for criteria that are too relaxed (Pincus 1991). For smaller r values, one usually achieves poor conditional probability estimates, while for larger r values, too much detailed system information is lost and SampEn tends to 0 for all processes.

Despite its advantages over ApEn, the use of SampEn is not widespread. It has been used to study abnormal heart rate (HR) characteristics of reduced variability in the early course of neonatal sepsis, where it has been shown that SampEn of neonatal HR falls before the clinical diagnosis of sepsis (Lake *et al* 2002). Moreover, this entropy measure has been applied to characterize the nonlinear features of HR time series for three recumbent positions (Kim *et al* 2005). To our knowledge, this is the first study of the EEG background activity with SampEn.

Because of the nonlinear character of EEG signals, SampEn can be used as a powerful tool in the study of the EEG background activity. For this study, SampEn was calculated with a short computer program, developed with MATLAB®, and parameter values $m = 1$ and $r =$ 0.25 times the standard deviation of the original data sequence. SampEn results for these set of values are in agreement with theoretical entropy estimates for short data sets as the EEG epochs we are analysing (Richman and Moorman 2000).

2.5. Statistical analysis

Student's *t*-test was used to evaluate the statistical differences between the estimated SpecEn and SampEn values for AD patients and control subjects. If the p value was lower than 0.01, the differences between the mean values were considered significant.

The ability of the entropy methods to discriminate AD patients from control subjects at the electrodes where $p < 0.01$ was evaluated using receiver operating characteristic (ROC) curves (Zweig and Campbell 1993). ROC curves can be obtained by plotting the sensitivity values (the proportion of patients with a diagnosis of AD who test positive, i.e. the true positive rate) on the y axis against their equivalent {1-specificity} values (specificity represents the percentage of controls correctly recognized, i.e. the true negative rate) for all the available cut-off points (in this case, the SpecEn or SampEn values) on the x axis. We used a computer program developed with MATLAB® that automatically selected different cut-off points and calculated the sensitivity/specificity pair for each one of them. Accuracy is a related parameter that quantifies the total number of subjects (AD patients and control subjects) precisely classified. The optimum threshold is the cut-off point in which the highest accuracy (minimal false negative and false positive results) is obtained. It can be determined from the ROC curve as the closest value to the left-top corner (100% sensitivity, 100% specificity).

3. Results

SpecEn and SampEn ($m = 1$, $r = 0.25$ times the standard deviation of the data) were estimated for channels Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5 and T6. The results were averaged based on all the artefact-free 5 s epochs ($N = 1280$ points) within the 5 min period of EEG recordings.

The SpecEn values (mean $\pm$ SD) for the AD patients and control subjects and the p values of the Student's *t*-tests performed to examine the differences between both groups are summarized in table 1. As can be seen, although the control subjects' spectral entropy values were higher than those of the AD patients at most electrodes, no significant differences were found between both groups ($p > 0.01$).

Table 2 summarizes the SampEn values (mean $\pm$ SD) for the AD patients and control subjects and the p values of the Student's *t*-test. AD patients had lower SampEn values than control subjects at all electrodes apart from T4, with significant differences between both groups at electrodes O1, O2, P3 and P4 ($p < 0.01$). These results suggest that EEG activity of AD patients is more regular (less complex) than in a normal brain in the parietal and occipital regions.

Finally, we evaluated the ability of SampEn to discriminate AD patients from control subjects at the electrodes in which significant differences were found using ROC plots (Zweig and Campbell 1993). The highest sensitivity was obtained at electrode O2 (90.91%), although with a small specificity (63.64%). On the other hand, the highest specificity was reached at electrode P4 (90.91%), with a decreased sensitivity (63.64%). The accuracy of the diagnostic test was similar at all four electrodes in which significant differences between both groups were

Table 1. Average SpecEn values of the EEGs for the AD patients and control subjects for all channels.

Electrode	Control subjects (mean ± SD)	AD patients (mean ± SD)	Statistical analysis (p value)
F3	0.6176 ± 0.0721	0.6207 ± 0.1024	0.9356
F4	0.6906 ± 0.0855	0.6477 ± 0.0938	0.2755
F7	0.6612 ± 0.1153	0.6758 ± 0.1027	0.7571
F8	0.7035 ± 0.1126	0.6746 ± 0.1064	0.5437
Fp1	0.6604 ± 0.1083	0.6302 ± 0.1216	0.5455
Fp2	0.6556 ± 0.1133	0.6094 ± 0.1011	0.3241
T3	0.7515 ± 0.0845	0.7102 ± 0.1176	0.3552
T4	0.7821 ± 0.0739	0.7110 ± 0.0926	0.0605
T5	0.7073 ± 0.0696	0.6726 ± 0.0735	0.2691
T6	0.7572 ± 0.1030	0.6629 ± 0.1244	0.0671
C3	0.6634 ± 0.1112	0.6273 ± 0.1143	0.4609
C4	0.6749 ± 0.1143	0.6165 ± 0.1281	0.2730
P3	0.7129 ± 0.0814	0.6383 ± 0.1144	0.0933
P4	0.7231 ± 0.0980	0.6416 ± 0.1027	0.0713
O1	0.7320 ± 0.0861	0.6822 ± 0.0802	0.1759
O2	0.7413 ± 0.0978	0.6769 ± 0.0729	0.0953

Table 2. Average SampEn(1, 0.25, 1280) values of the EEGs for the AD patients and control subjects for all channels. Significant group differences are marked with an asterisk.

Electrode	Control subjects (mean ± SD)	AD patients (mean ± SD)	Statistical analysis (p value)
F3	0.6551 ± 0.1867	0.5759 ± 0.1048	0.2342
F4	0.6473 ± 0.1796	0.6357 ± 0.1237	0.8610
F7	0.7030 ± 0.1859	0.6694 ± 0.1450	0.6425
F8	0.7162 ± 0.1645	0.6636 ± 0.1425	0.4325
Fp1	0.6533 ± 0.1471	0.5177 ± 0.1803	0.0677
Fp2	0.6371 ± 0.1966	0.5279 ± 0.1196	0.1316
T3	0.8783 ± 0.2697	0.8481 ± 0.2275	0.7798
T4	0.8513 ± 0.2254	0.8629 ± 0.3003	0.9189
T5	0.8284 ± 0.1835	0.6329 ± 0.1867	0.0223
T6	0.8141 ± 0.1908	0.6327 ± 0.1972	0.0404
C3	0.7578 ± 0.1484	0.6652 ± 0.1794	0.2020
C4	0.7670 ± 0.1178	0.7040 ± 0.1987	0.3765
P3*	0.7781 ± 0.1201	0.5576 ± 0.1625	0.0017
P4*	0.7852 ± 0.1192	0.5859 ± 0.1547	0.0029
O1*	0.8849 ± 0.1672	0.6361 ± 0.1745	0.0027
O2*	0.8538 ± 0.1899	0.6278 ± 0.1756	0.0089

found (77.27%). However, sensitivity was higher than specificity on the occipital electrodes, while specificity was higher than sensitivity on the parietal channels. Table 3 summarizes these results.

The value for the area under the ROC curve can be interpreted as follows: an area of 0.8595 (electrode O1, for example) means that a randomly selected individual from the control subjects' group has a SampEn value larger than that of a randomly chosen individual from the AD patients' group in 85.95% of the time (Zweig and Campbell 1993). A rough guide

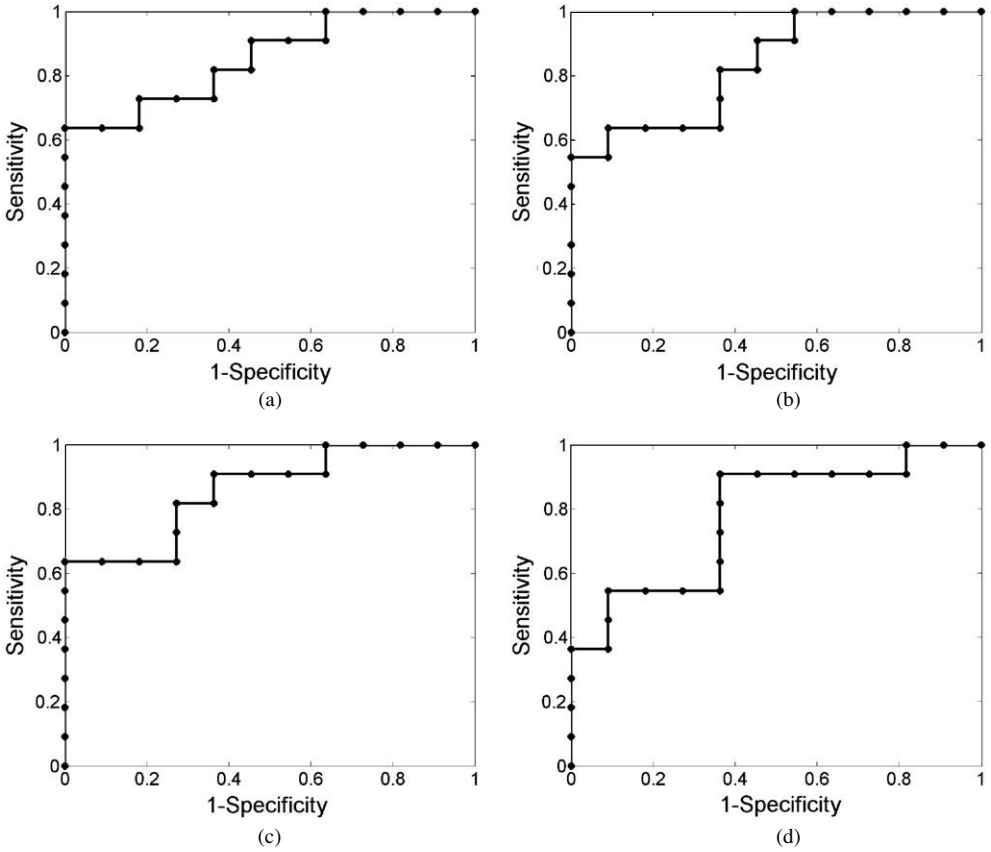

Figure 1. ROC curves for the SampEn values at the electrodes in which $p < 0.01$. (a) P3. (b) P4. (c) O1. (d) O2.

Table 3. Test results for SampEn(1, 0.25, 1280) on the channels in which the differences between both groups were significant. The optimum threshold to discriminate AD patients and control subjects is included.

Electrode	Threshold	Sensitivity (%)	Specificity (%)	Accuracy (%)	Area under the ROC curve
P3	0.6658	72.73	81.82	77.27	0.8512
P4	0.6740	63.64	90.91	77.27	0.8347
O1	0.7492	81.82	72.73	77.27	0.8595
O2	0.7367	90.91	63.64	77.27	0.7769

to classify the precision of a diagnostic test is related to the area under the ROC curve. With values between 0.90 and 1, the precision of the diagnostic test is considered to be excellent, good for values between 0.80 and 0.89, fair if the results are in the range 0.70–0.79, poor when the value of the area under the ROC curve is between 0.60 and 0.69 and bad for values between 0.50 and 0.59. Thus, the results obtained can be considered good for electrodes P3, P4 and O1, and fair for electrode O2. Figure 1 depicts the ROC curves corresponding to the SampEn analysis.

4. Discussion and conclusions

In this pilot study, we have analysed the EEG background activity of 11 control subjects and 11 patients with AD applying SampEn and SpecEn. SampEn is an embedding entropy related to ApEn. SampEn statistics provide an improved evaluation of time series irregularity, with increasing values corresponding to intuitively increasing process complexity. SpecEn is the Shannon entropy formula suitably normalized and applied to the power spectral density of the signal, and is a convenient way of quantifying the distribution of spectral power.

SpecEn has proven not to be effective in discriminating AD patients from control subjects. Although the mean SpecEn values were higher at most electrodes for control subjects than for AD patients, the differences were not significant ($p > 0.01$). One of the most relevant EEG abnormalities in AD patients is a shift of the power spectrum to lower frequencies, through increase of the delta (0.5–4 Hz) and theta (4–8 Hz) power, along with decrease of the alpha (8–13 Hz) power (Jeong 2004). SpecEn quantifies the distribution of spectral power in the EEG. However, our results show that, contrary to what we expected, SpecEn is unable to reflect the power spectrum changes usually found in AD. This might be due to the fact that the spectral distribution of power in the EEG of AD patients is shifted to lower frequencies, but the shape of the spectrum remains relatively unchanged. Despite these negative results, the possible usefulness of SpecEn in the diagnosis of AD should be investigated with a larger number of patients and control subjects.

On the other hand, we have found that AD patients have significantly lower SampEn values than control subjects at electrodes O1, O2, P3 and P4 ($p < 0.01$). We infer that brains affected by AD show a more regular and less complex electrophysiological behaviour in the parietal and occipital regions. This confirms findings associated with the fact that a diffuse slowing of the background activity may be found in the EEG of patients with AD (Markand 1990). Moreover, our results agree with other studies showing that the EEG of AD patients has lower D_2 values than that of control subjects (Pritchard *et al* 1994, Stam *et al* 1995, Jeong *et al* 1998, 2001a, Jelles *et al* 1999) and, consequently, a less complex brain activity. Besthorn *et al* (1995) found that a lower D_2 was correlated with increased severity of dementia and that this method correctly classified AD patients and controls with an accuracy of 70% (Besthorn *et al* 1997). Pritchard *et al* (1994) showed that the addition of nonlinear measures (D_2) and a neural net classification procedure to linear methods improves the classification accuracy of the AD/control status of subjects up to 92%. Jeong *et al* (1998, 2001a) found that AD patients have significantly lower $L1$ values than age-matched controls. $L1$ of the EEG can be interpreted as a measure of flexibility of information processing in the brain (Röschke *et al* 1995). In this context, decreased $L1$ values in AD patients reflect a drop in the flexibility of information processing in the injured brain (Jeong 2004). The decreased complexity of brain activity in AD patients has also been shown using Lempel–Ziv complexity (Abásolo *et al* 2005b), with an accuracy of 81.82% at some electrodes. Furthermore, the aforementioned increased regularity in the EEG background activity in AD patients has also been found in the parietal electrodes with ApEn (Abásolo *et al* 2005a). The results of this study suggest that ApEn might be complementary to spectral and autocorrelation analyses.

The reduction of irregularity in the EEG of AD patients could be explained by a decrease of dynamical complexity of part of the brain. However, the pathophysiological implications of this decreased EEG irregularity (or complexity) are not clear. Among others, three mechanisms can be responsible for it: neuronal death, a general effect of neurotransmitter deficiency and loss of connectivity of local neural networks as a result of nerve cell death (Jelles *et al* 1999, Jeong 2004). Nevertheless, ageing and age-related diseases often accompany

a wide-ranging loss of physiological complexity (Kyriazis 2003). As the AD patients' and control subjects' groups were carefully matched for age, the increase of regularity in the parietal and occipital regions might represent the cognitive dysfunction in AD. However, a possible association should be investigated with a larger number of patients and control subjects.

In order to estimate SampEn accurately we need recordings of just 10^m to 20^m points, where m is the run length that must be fixed to compute this embedding entropy. Thus, this family of statistics is much better suited for EEG analysis than traditional nonlinear techniques such as $L1$ or D_2 that require an amount of data to obtain meaningful results usually beyond the experimental possibilities for physiological data (Eckmann and Ruelle 1992). Moreover, SampEn statistics (Richman and Moorman 2000)

- agree much better than ApEn with theory for random numbers with known probabilistic character over a broad range of operating conditions,
- maintain relative consistency where ApEn statistics do not and
- have residual bias for very short record lengths.

These properties make SampEn an attractive tool for nonlinear analysis of biomedical signals.

Some limitations of our study merit consideration. First of all, although AD patients had lower SampEn values than control subjects at all electrodes apart from T4, only four electrodes (P3, P4, O1 and O2) showed statistically significant differences between both groups. The symmetric disposition of those electrodes over the scalp shows promise and might reflect significant changes in the brain electrical activity of AD patients in the parietal and occipital regions. However, caution should be applied due to the preliminary nature of this study. Furthermore, the sample size was small. Hence, to prove the usefulness of SampEn as a diagnostic tool, this approach should be extended on a much larger patient population. Moreover, the detected increase of EEG regularity (or decrease of complexity) is not specific to AD. It appears in several physiological and pathological states including, among others, sleep (Burioka *et al* 2003), anaesthesia (Zhang and Roy 2001), the Creutzfeld-Jakob disease (Babloyantz and Destexhe 1988), vascular dementia (Jeong *et al* 1998), schizophrenia (Röschke *et al* 1995) and Parkinson's disease (Stam *et al* 1995). Thus, although this pilot study shows that SampEn might be a helpful tool for recognition of AD, further work must be carried out to examine nonlinear EEG activity in other types of dementia.

In summary, although nonlinear EEG analysis cannot yet be applied as a diagnostic tool, our findings show the possibility of analysing the dynamical behaviour of the brain in AD patients and detecting significant differences with SampEn. Our experimental results prove the potential applications of this new family of statistics in reflecting differences in the irregularity of EEG data time series of patients with a diagnosis of AD and control subjects. Nonlinear dynamics suggest that AD can be a dynamical disease which is characterized by changes in the qualitative dynamics of physiological processes (Belair *et al* 1995). The decrease of the EEG entropy found in the parietal and occipital regions in AD patients leads us to think that EEG analysis with SampEn could be a useful tool to increase our insight into brain dysfunction in this disease.

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