Analysis of electroencephalograms in Alzheimer's disease patients with multiscale entropy

Analysis of electroencephalograms in Alzheimer's disease patients with multiscale entropy

J Escudero[1], D Abásolo[1], R Hornero[1], P Espino[2] and M López[1]

[1] E.T.S. Ingenieros de Telecomunicación, University of Valladolid, Camino del Cementerio s/n, 47011, Valladolid (Spain)
[2] Hospital Clínico San Carlos, c/Profesor Martín Lagos s/n, 28040, Madrid (Spain)

E-mail: jescrod@gmail.com

Abstract
The aim of this study was to analyse the electroencephalogram (EEG) background activity of Alzheimer's disease (AD) patients using the Multiscale Entropy (*MSE*). The *MSE* is a recently developed method that quantifies the regularity of a signal on different time scales. These time scales are inspected by means of several coarse-grained sequences formed from the analysed signals. We recorded the EEGs from 19 scalp electrodes in 11 AD patients and 11 age-matched controls and estimated the *MSE* profile for each epoch of the EEG recordings. The shape of the *MSE* profiles reveals the EEG complexity, and it suggests that the EEG contains information in deeper scales than the smallest one. Moreover, the results showed that the EEG background activity is less complex in AD patients than control subjects. We found significant differences between both subject groups at electrodes F3, F7, Fp1, Fp2, T5, T6, P3, P4, O1 and O2 (p-value < 0.01, Student's t-test). These findings indicate that the EEG complexity analysis performed on deeper time scales by the *MSE* may be a useful tool in order to increase our knowledge of AD.

Keywords: Alzheimer's disease, electroencephalogram, multiscale entropy, complexity, time scales

PACS number(s): 05.45.Tp, 87.19.La, 87.80.Tq

1. Introduction

Alzheimer's disease (AD) is the most frequent cause of dementia in western countries (Bird 2001): approximately 50-60% of patients with dementia over 65 years are clinically related with AD and the number of patients is expected to increase continuously (Lahiri *et al* 2002).

AD is characterized by generalized neuronal cell loss, neurofibrillary tangles inside the cells and senile plaques among the neurons in different brain regions. Reduced brain weight, cortical atrophy and ventricular enlargement are also important deficiencies in the brain of AD patients. All these neuropathologies cause progressive cognitive and intellectual deficits and behaviour disturbance (Bird 2001).

AD can only be diagnosed without any probability of error by necropsy, but a differential diagnosis with other types of dementia and major depression is usually attempted. Mental status test, such as the Folstein's Mini Mental State Examination (MMSE) (Folstein *et al* 1975), are frequently used in order to help to determine the severity of the dementia, and methods of medical imaging, such as magnetic resonance imaging or computed tomography, can also be

useful in diagnosis in medium stages of the AD. In order to complete the diagnosis, the use of the EEG as a diagnostic tool for AD and other kinds of dementia has been researched for several decades (Jeong 2004). Simple conventional visual analysis of the EEG in AD patients has demonstrated a slowing of the dominant posterior rhythm, an increase in diffuse slow activity, a reduction in beta and alpha activities and a decreased coherence among cortical areas (Jeong 2004). However, in the early stages of AD the frequencies of the EEG may look normal (Markand 1990). On the other hand, computerized EEG spectral analysis has also shown a decrease in the mean frequency and an increase in delta and theta bands power with a simultaneous decrease in alpha and beta power in AD patients (Jeong 2004). In general, the severity of the cognitive impairments and the degree of the EEG abnormalities are correlated (Jeong 2004).

Until the introduction of new analysis methods derived from non-linear dynamics, the only tools which were available to analyse EEG signals were the linear techniques based on coherence and spectral calculations (Jeong 2004). Nevertheless, the ability of the brain to perform sophisticated cognitive tasks supports the hypothesis that the brain may not be completely stochastic (Zhang *et al* 2001). Furthermore, the neurons are governed by non-linear phenomena, like the threshold and saturation processes, so the behaviour of the brain can be classified as non-linear. Based on these hypotheses, the non-linear dynamical techniques may provide more suitable methods than the traditionally used linear tools to understand and characterize pathologic brain states by means of the EEG activity examination.

The first non-linear analysis techniques applied to EEGs were the correlation dimension (D_2) (Grassberger and Procaccia 1983a) and the first Lyapunov exponent (L_1) (Wolf *et al* 1985). D_2 quantifies the number of independent variables which are necessary to describe the dynamic of the system, so higher D_2 values have been related to more complex systems. Several studies have proven that D_2 can provide potentially useful diagnostic information from mental diseases using both time time-delay (Babloyantz and Destexhe 1988, Besthorn *et al* 1995, Hornero *et al* 1999, Jeong *et al* 1998) and spatial embedding (Stam *et al* 1995) methods to reconstruct the attractor. In AD, the widespread loss of synapses and neurons may produce lower D_2 values, as several studies have proven (Jelles *et al* 1999, Jeong *et al* 1998, 2001a, Stam *et al* 1995). Whereas D_2 provides a static characterization of the system, L_1 is a relatively dynamic measure, since it describes the divergence of trajectories that start at similar initial states (Wolf *et al* 1985). L_1 is usually interpreted as a measure of the flexibility of the system to reach different states from almost identical initial states. A few studies (Jeong *et al* 1998, Stam *et al* 1995) have also revealed the potential usefulness of L_1 in the diagnosis of AD.

Nevertheless, the application of both D_2 and L_1 on physiological data has some major problems. First, the amount of data required to obtain meaningful results is beyond the length of the physiological data that can be collected experimentally (Eckmann and Ruelle 1992). Besides, the algorithms used to estimate the D_2 require the recordings to be stationary, something that is almost impossible when working with biological data (Grassberger and Procaccia 1983b).

Due to these major drawbacks of D_2 and L_1, it becomes necessary to use other non-linear methods to study the EEG background activity. Several of these alternative methods are based on the concept of "complexity". Roughly speaking, complexity is related to "meaningful structural richness" (Costa *et al* 2005). Several studies associate complexity with irregularity or with the ability of the systems to create information. For instance, the Approximate Entropy (*ApEn*) (Pincus 1991) quantifies the regularity of a time series by evaluating the appearance of repetitive patterns. *ApEn* has been used on biological data providing potentially useful information to diagnose different pathological states (Hornero *et al* 2005, Pincus 2001). Another complexity measure that has been extensively applied to biological data is the Lempel-Ziv (*LZ*) Complexity (Lempel and Ziv 1976). *LZ* complexity is related to the number of distinct substrings and the rate of their recurrence along the analysed signal, with larger values corresponding to more "complex" data (Lempel and Ziv 1976). Both *ApEn* and *LZ* complexity have been already used to analyse EEGs of several brain states (Abásolo *et al* 2005, 2006b,

Ferenets *et al* 2006, Radhakrishnan and Gangadhar 1998, Zhang *et al* 2001, Zhang and Roy 2001).

On the other hand, for other authors "complexity" has a more restricted meaning. In this context, complex systems are neither absolutely regular nor absolutely random (Costa *et al* 2005, López-Ruiz *et al* 1995, Tononi *et al* 1998). Although measures like *ApEn* or *LZ* complexity have shown potentially useful results, they return high values when they are applied to random data (Hornero *et al* 2005). Thus, such kind of statistics would be not strictly complexity measures, but regularity estimators (Goldberger *et al* 2002). From this point of view a complexity measure should vanish for both completely regular and completely random system (Costa *et al* 2005, López-Ruiz *et al* 1995, Tononi *et al* 1994). Estimators of complexity which satisfy this requirement were introduced in (Costa *et al* 2002, López-Ruiz *et al* 1995, Tononi *et al* 1994). In this paper we adopt this idea of "complexity".

A new complexity measure that fulfils the requirement of vanishing for absolutely random or regular systems was proposed in Costa *et al* (2002). This complexity measure is the Multiscale Entropy (*MSE*) (Costa *et al* 2002, Costa *et al* 2005). *MSE* has been proposed to give potentially useful information for diagnosis (Costa *et al* 2005, Ferrario *et al* 2006) or to analyse complex biological systems (Bhattacharya *et al* 2005). *MSE* focuses on determining the information expressed by the signals on multiple time scales, and it has the advantage of being applicable to series of finite length (Costa *et al* 2005).

In this pilot study we have examined the EEG background activity in AD patients and age-matched control subjects using the *MSE*. We wanted to test the hypothesis that the *MSE* analysis of EEG background activity might differentiate AD patients from control subjects.

This paper is organized as follows. In section 2 we explain the selection of patients and controls, and how the EEG was recorded and reviewed by a specialist physician to get artefact-free epochs. The *MSE* and the statistical analysis carried out are also introduced in this section. Section 3 summarizes our results. Finally, in Section 4 we discuss the results previously presented and we relate them with other studies of EEG background activity in AD patients with non-linear analysis method. We present our conclusions in the last part of this paper.

2. Materials and Methods

2.1. Selection of patients and control subjects

In the current pilot study, the EEG was recorded from 11 AD patients and 11 control subjects. The 11 patients − 5 men and 6 women; age = 72.5 ± 8.3 years, mean ± standard deviation (SD) − were recruited from Alzheimer's Patients' Relatives Association of Valladolid (AFAVA). All of them fulfilled the criteria of probable AD. The EEG was registered in the University Hospital of Valladolid (Spain) after all the patients had undergone a meticulous clinical evaluation which included clinical history, neurological and physical examinations, brain scans and a MMSE in order to evaluate their cognitive ability (Folstein *et al* 1975). Although the mean MMSE score for the AD group was 13.1 ± 5.9 points (mean ± SD), indicating that the average degree of the disease is moderate, five patients had a MMSE score below 12 points, and therefore their degree of dementia is severe. Two subjects were having a lorapezam treatment, which may enhance beta activity with therapeutic doses, although no prominent rapid rhythms were observed in the visual inspection of these two subjects' EEG recordings. The other patients did not use any medication that could be expected to influence the EEG.

The 11 age-matched, elderly subjects who made up the control group had not got any past or present mental disorder − 7 man and 4 women; 72.8 ± 6.1 years ± SD −. The MMSE score values for all of them were 30.

The local ethics committee approved the study. All control subjects and all caregivers of the patients gave their informed consent for participation in the current study. An EEG was recorded from all patients and controls.

2.2. EEG recording

The EEG data were recorded from each subject by a Profile Study Room 2.3.411 EEG equipment (Oxford Instruments) at electrodes F3, F4, F7, F8, Fp1, Fp2, T3, T4, T5, T6, C3, C4, P3, P4, O1, O2, Fz, Cz and Pz of the international 10-20 system. More than 5 minutes of EEG data were recorded from each subject. While the recording process was taking place, the subjects were asked to remain in a relaxed state, with closed eyes and awake in order to reduce the presence of artefacts in the recordings. EEG data were sampled at 256 Hz, with a 12 bits A-to-D precision.

The recordings were visually inspected by a specialist physician to select data with minimal movement, electromyographic activity or electrooculographic artefacts. Artefact-free epochs of 5 s (1280 points) were chosen from the EEG data. Thus, an average number of 30.0 ± 12.5 artefact-free epochs (mean ± SD) were selected at each electrode for each one of the subjects.

These data were copied to ASCII files for off-line analysis on a personal computer. Before the nonlinear analysis, the selected epochs were digitally filtered with a bandpass filter with cut-off frequencies at 0.5 Hz and 40 Hz developed with MATLAB®.

2.3. Multiscale Entropy (MSE)

MSE was introduced as a tool to achieve a quantification of the signal complexity considering several time scales (Costa *et al* 2002). It is based on successive computations of the Sample Entropy (*SampEn*) (Richman and Moorman 2000) estimated on coarse-grained sequences, each of which represents the system dynamics on a different time scale. The use of the *SampEn* has important positive aspects: it is independent of the sequence length and the model. Moreover, it can be applied to relatively short, noisy data sets (Richman and Moorman 2000).

Formally, given a one-dimensional discrete time series, $\{x_1, \ldots, x_i, \ldots, x_N\}$, first we must build successive coarse-grained time series, $\{Y^{(\tau)}\}$, corresponding to the scale factor τ. To accomplish this task, we divide the original time series into non-overlapping windows of length τ, and then we average the values of the data points inside each window. It is possible to summarize this process (Costa *et al* 2005) in the following way:

$$Y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i \,, \quad 1 \le j \le \frac{N}{\tau} = N^{(\tau)}. \qquad (1)$$

Obviously, the coarse-grained sequence for time scale $\tau = 1$, $\{Y^{(1)}\}$, is simply the original time series, and the length of each coarse-grained sequence is τ times shorter than the length of the original signal.

Once those coarse-grained time series are built, we calculate their *SampEn*, which assigns a non-negative value to each coarse-grained sequence. This procedure is called multiscale entropy analysis (Costa *et al* 2005). Briefly, *SampEn* measures the negative of the logarithmic conditional probability that sets of patterns which are closer than a tolerance, *r*, for *m* contiguous points remain similar at the next point (pattern length *m*+1), where self-matches are not included in calculating the probability. More irregularity in the data produces larger *SampEn* values (Richman and Moorman 2000). The algorithm that computes the *SampEn* can be found in Richman and Moorman (2000), Costa *et al* (2005) or Abásolo *et al* (2006a).

Like *ApEn* or *SampEn*, the values of *m* and *r* are critical in the performance of *MSE*, and comparisons between time series can only be done with values of *m*, *r* and *N* unchanged (Costa *et al* 2005). However, there are no guidelines to determine the optimum values for *m* and *r*. In order to avoid a significant contribution of noise in the estimation of *SampEn*, *r* must be higher than most of the signal noise (Pincus 1991). In addition, if a too narrow tolerance (too small *r*) is used, the estimation of the *SampEn* might fail. The reason is that runs of *m*+1 points that match continuous patterns of *m* points may not be found if *r* is too small and the analysed time series is not large. Furthermore, the accuracy and confidence of the *SampEn* improve as smaller

values for m (short templates) and larger values for r (wide tolerance) are used, since the number of matches of length m and m+1 increases (Lake *et al* 2002). However, some problems may arise when the matching criteria is too relaxed (Pincus 1991). It is convenient to normalize the tolerance by the standard deviation of the original time series (Costa *et al* 2005). Nikulin and Brismar (2004) have recently indicated that the *MSE* profiles are sensitive to both variance and entropy because the effective filter, r, is fixed but not normalized for the estimation of the *SampEn* on larger time scales. However, the entropy of a sequence depends on both its variance and correlation properties (Costa *et al* 2004), and there is no straightforward relationship between variance and entropy for non-trivial signals (Costa et al 2005). Hence, the value of the r parameter should not be normalized again in larger time scales because the changes of the variance of the coarse-grained sequences have information about the whole original signal (Costa *et al* 2005).

In this study we have chosen $m = 1$ and $r = 0.25$ times the standard deviation of the original time series. This set of parameters has been used in a previous study of EEG background activity in AD patients using *SampEn* (Abásolo *et al* 2006a). The maximum analysed time scale was $\tau_{MAX} = 12$. In such a way, the shortest coarse-grained sequence built has more than 100 points. Our selection of the m and r parameters is able to produce good statistical reproducibility when the length of the analysed series is larger than 100 points, as the coarse-grained sequences we are considering (Lake *et al* 2002).

Owing to the non-linear character of the EEG signals and several studies related with AD and non-linear dynamics (Abásolo *et al* 2005, 2006a, b, Jelles *et al* 1999, Jeong *et al* 1998, 2001a, Pritchard *et al* 1994, Stam *et al* 1995), we hope that *MSE* could be used as a tool to discover differences in the background EEG activity of patients of AD against control subjects. In order to obtain information from the deeper time scales not yet explored, we represent the *SampEn* values versus the time scale (Costa *et al* 2005).

Is this pilot study the calculations of *MSE* from the EEG signals were carried out with a software developed with MATLAB®.

2.4. Statistical analysis

Student's t-test was used to evaluate the statistical differences between the *MSE* of AD patients and control subjects. If the p-value was lower than 0.01, the differences were considered significant. In addition, correlations between AD patients' MMSE scores and the parameters that provided significant differences between both groups were computed with Pearson's correlation coefficient (ρ). We also calculated the corresponding p-values for testing the hypothesis of no correlation against the alternative that there is a non-zero correlation. The correlation was considered significant when the p-value was below 0.01.

Moreover, we used Receiver Operating Characteristic (ROC) curves (Zweig and Campbell 1993) to evaluate the ability of the *MSE* in discriminating AD patients from control subjects at the electrodes where p-value < 0.01. ROC curves are 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 possible set of cut-off points. 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

The *MSE* algorithm was applied for channels F3, F4, F7, F8, Fp1, Fp2, T3, T4, T5, T6, C3, C4, P3, P4, O1 and O2 with $m = 1$ and $r = 0.25$ times the standard deviation of the original time series. These results were averaged based on all the artefact-free 5 s epochs within the 5-min period of EEG recordings.

We performed a visual inspection of the obtained *MSE* profiles representing the *SampEn* values of each coarse-grained sequence versus the scale. We could see that these *MSE* profiles were characterized by a steep slope on the smaller time scales. Next, the slope decreased and the *SampEn* values were approximately constant on the larger time scales. Thus, it is possible to divide the *MSE* profiles into two parts: the first one corresponds to the steep increasing slope, whereas the second part contains the time scales where the slope of the *SampEn* values is much smoother. In order to characterize every *MSE* profile and hence, every EEG recording:

a) We estimated the slope of the *MSE* profile for $1 \leq \tau \leq 5$ ($t \leq 20$ ms). It shows how the EEG complexity evolves for small time scales.
b) Similarly, the slope of the *MSE* profile for $6 \leq \tau \leq 12$ ($t \geq 23$ ms) was calculated. It provides information about the increase or decrease of the *MSE* profile for large time scales.

Both slopes were estimated by means of the least square method.

We computed the average slope values of the *MSE* profiles for small time scales and calculated the *p*-values of the Student's *t*-test to determine whether there exist significant differences between both groups. Table 1 summarizes the results (Mean ± SD) and the *p*-values. No significant differences were found (*p*-value > 0.01).

Table 1. Average slope values of the *MSE* profiles for small time scales ($\tau \leq 5$) of the EEGs for both groups for all channels with $m = 1$ and $r = 0.25$ times the standard deviation of the original data sequence.

Electrode	AD patients (Mean ± SD)	Control subjects (Mean ± SD)	Statistical analysis
			p-value
F3	0.1971 ± 0.0361	0.1841 ± 0.0325	0.3843
F4	0.2017 ± 0.0268	0.1841 ± 0.0238	0.1197
F7	0.1789 ± 0.0407	0.1849 ± 0.0309	0.7049
F8	0.1821 ± 0.0379	0.1810 ± 0.0315	0.9410
Fp1	0.1684 ± 0.0437	0.1805 ± 0.0308	0.4613
Fp2	0.1812 ± 0.0281	0.1794 ± 0.0291	0.8867
T3	0.1623 ± 0.0479	0.1644 ± 0.0369	0.9062
T4	0.1499 ± 0.0617	0.1688 ± 0.0332	0.3822
T5	0.2062 ± 0.0220	0.1950 ± 0.0379	0.4048
T6	0.2035 ± 0.0294	0.1945 ± 0.0353	0.5226
C3	0.1956 ± 0.0353	0.1911 ± 0.0304	0.7494
C4	0.1927 ± 0.0428	0.1936 ± 0.0328	0.9542
P3	0.2181 ± 0.0193	0.2094 ± 0.0318	0.4458
P4	0.2236 ± 0.0179	0.2115 ± 0.0378	0.3508
O1	0.2060 ± 0.0288	0.1907 ± 0.0435	0.3434
O2	0.2083 ± 0.0278	0.1888 ± 0.0422	0.2172

There were important differences between the *MSE* profiles of control subjects and AD patients. First, whereas the irregularity of the coarse-grained time series decreased on the larger time scales in the control group, the coarse-grained sequences of the AD patients were usually slightly more irregular as we analyse larger time scales. Therefore, the maximum *SampEn* value was usually reached on smaller time scales in the control subjects than in AD patients. Furthermore, the *SampEn* values were higher for control subjects than for AD patients, apart from the largest time scales, suggesting that the control subjects have a more complex EEG background activity than the AD patients (Costa *et al* 2005). The averaged *MSE* profiles for the control subjects and AD patients for all electrodes are shown in figure 1.

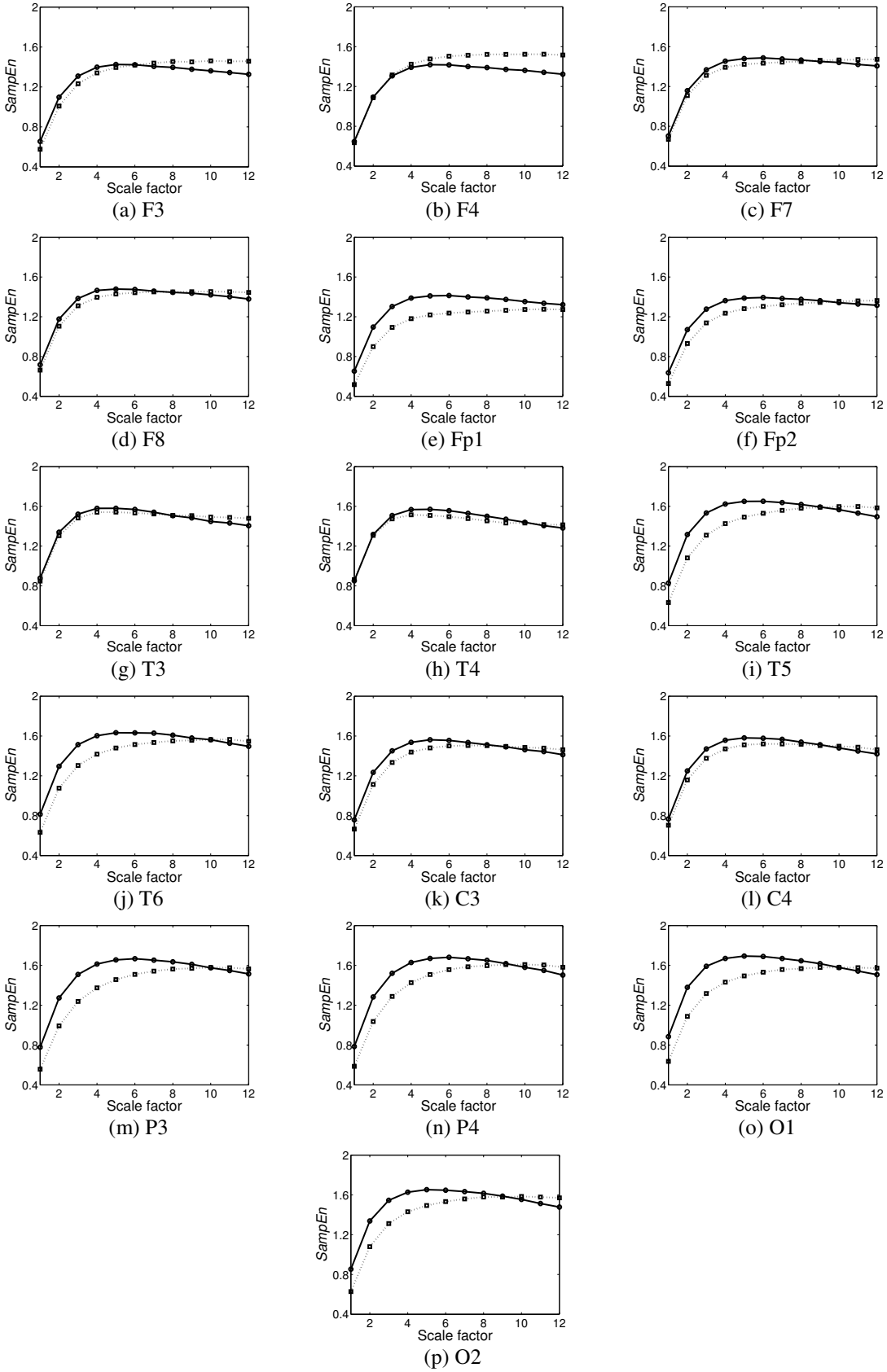

Figure 1. *MSE* analysis of the 11 control subjects (full curve) and the 11 AD patients (dotted curve) with $m = 1$ and $r = 0.25$ times the standard deviation of the original data sequence. Sixteen electrodes of the international 10-20 system were analysed. (a) F3. (b) F4. (c) F7. (d) F8. (e) Fp1. (f) Fp2. (g) T3. (h) T4. (i) T5. (j) T6. (k) C3. (l) C4. (m) P3. (n) P4. (o) O1. (p) O2.

Table 2 summarizes the average slopes (Mean ± SD) of the *MSE* profiles for AD patients and control subjects for large time scales ($\tau \geq 6$), along with the *p*-values of the Student's *t*-test. Whereas this slope decreases at all electrodes for the control subjects, the AD patients have an increasing slope at all electrodes except for T3, T4, C3 and C4. At ten electrodes significant differences between both groups have been found: F3, F7, Fp1, Fp2, T5, T6, P3, P4, O1 and O2 (*p*-values < 0.01).

Table 2. Average slope values of the *MSE* profiles for large time scales ($\tau \geq 6$) of the EEGs for both groups for all channels with $m = 1$ and $r = 0.25$ times the standard deviation of the original data sequence. Significant group differences are marked with an asterisk.

Electrode	AD patients (Mean ± SD)	Control subjects (Mean ± SD)	Statistical analysis
			p-value
F3*	0.0056 ± 0.0141	-0.0159 ± 0.0159	0.0032
F4	0.0021 ± 0.0144	-0.0152 ± 0.0162	0.0156
F7*	0.0067 ± 0.0116	-0.0135 ± 0.0184	0.0061
F8	0.0004 ± 0.0199	-0.0152 ± 0.0117	0.0359
Fp1*	0.0065 ± 0.0097	-0.0158 ± 0.0135	0.0002
Fp2*	0.0098 ± 0.0101	-0.0135 ± 0.0174	0.0010
T3	-0.0089 ± 0.0251	-0.0273 ± 0.0254	0.1018
T4	-0.0139 ± 0.0342	-0.0297 ± 0.0175	0.1888
T5*	0.0092 ± 0.0202	-0.0260 ± 0.0186	0.0004
T6*	0.0061 ± 0.0208	-0.0234 ± 0.0166	0.0015
C3	-0.0067 ± 0.0173	-0.0237 ± 0.0213	0.0532
C4	-0.0092 ± 0.0218	-0.0275 ± 0.0221	0.0652
P3*	0.0089 ± 0.0206	-0.0259 ± 0.0185	0.0005
P4*	0.0043 ± 0.0245	-0.0299 ± 0.0194	0.0017
O1*	0.0061 ± 0.0206	-0.0309 ± 0.0157	0.0001
O2*	0.0055 ± 0.0230	-0.0289 ± 0.0189	0.0010

Moreover, we assessed whether the severity of the dementia was correlated with the changes in the average slope values of the *MSE* profiles for large time scales at the electrodes which provided significant differences between both subjects groups. Thus, we computed the ρ values between the AD patients' MMSE scores and their average slope values for $\tau \geq 6$ at electrodes F3, F7, Fp1, Fp2, T5, T6, P3, P4, O1 and O2. The results showed that none of the correlations was significant (*p*-values > 0.01).

Finally, we evaluated the ability of the slope for large time scales to discriminate AD patients from control subjects at the electrodes in which significant differences were found using ROC plots. Figure 2 depicts the corresponding ROC curves. These curves allowed us to determine the optimum threshold (value of the slope for the largest time scales) to classify subjects from both groups. According to these optimum thresholds, the minimum accuracy of the diagnostic test was obtained at electrode F7 (77.27%), while the maximum value was reached at Fp1 (90.91%). The highest sensitivity was reached at Fp2 (100%; i.e. all AD patients were correctly classified), although with a small specificity (72.73%). On the other hand, the highest specificity was reached at electrodes Fp1, P3, P4 and O1 (90.91%). Another interesting parameter that can be obtained from ROC plots is the area under the curve. The value for the area under the ROC curve can be interpreted as follows: an area of 0.9174 (electrode O1, for example) means that a randomly selected individual from the control subjects' group has a slope value smaller than that of a randomly chosen individual from the AD patients' group in 91.74% of the time (Zweig and Campbell 1993). In general, the larger the area under the curve, the better the diagnostic test. The largest area under the curve was obtained at Fp1 (0.9339), which is the electrode where the highest accuracy was obtained. Table 3 summarizes these results.

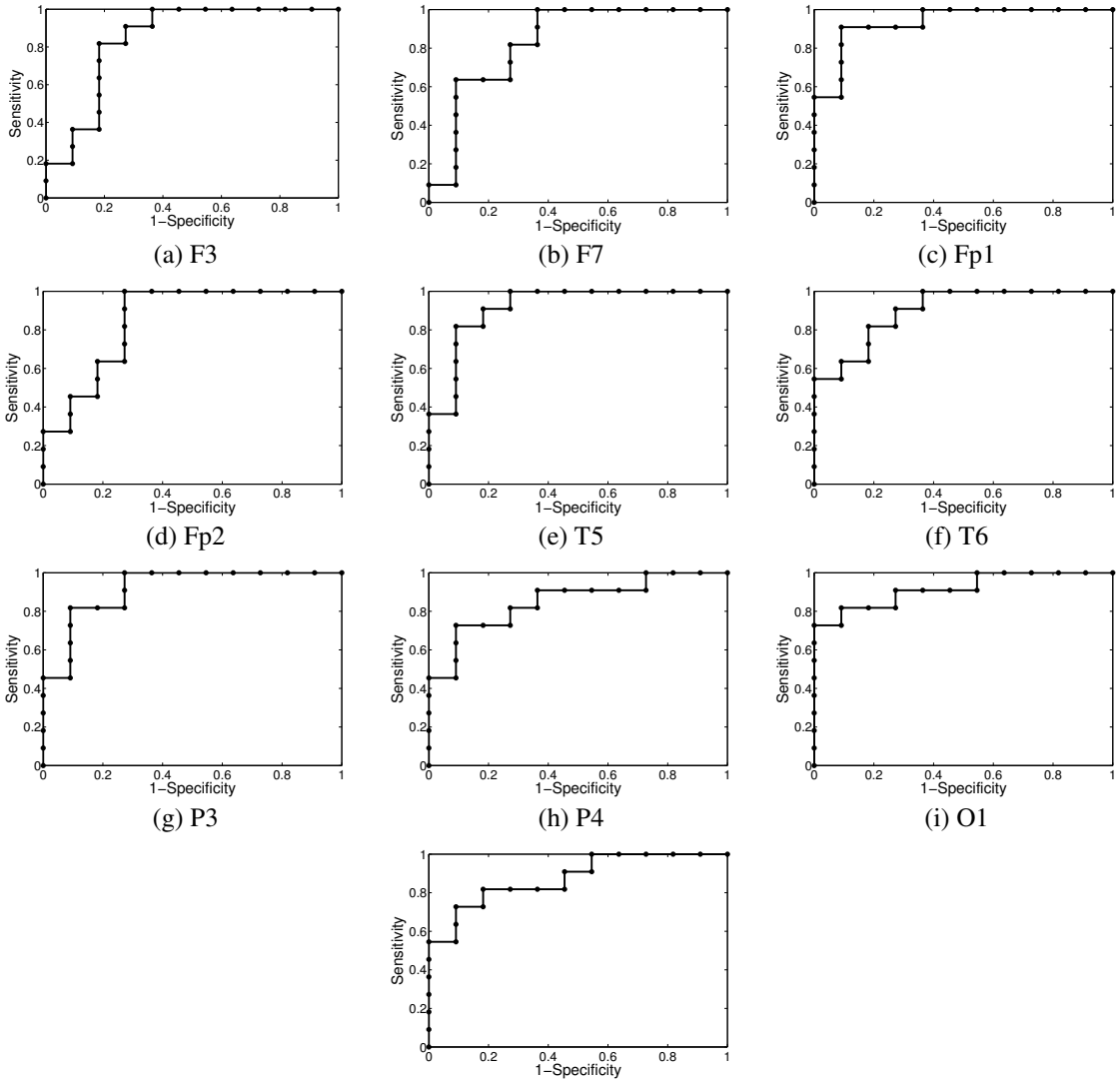

Figure 2. ROC curves for the average slope values of the *MSE* profiles for large time scales ($\tau \geq 6$) with $m = 1$ and $r = 0.25$ times the standard deviation of the original data sequence at the electrodes in which p-value < 0.01. (a) F3. (b) F7. (c) Fp1. (d) Fp2. (e) T5. (f) T6. (g) P3. (h) P4. (i) O1. (j) O2.

Table 3. Test results for the slope of the *MSE* profiles ($\tau \geq 6$) 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
F3	-0.0037	81.82	81.82	81.82	0.8430
F7	-0.0020	81.82	72.73	77.27	0.8347
Fp1	-0.0026	90.91	90.91	90.91	0.9339
Fp2	-0.0113	100	72.73	86.36	0.8512
T5	-0.0167	90.91	81.82	86.36	0.9174
T6	-0.0155	81.82	81.82	81.82	0.9008
P3	-0.0119	81.82	90.91	86.36	0.9174
P4	-0.0097	72.73	90.91	81.82	0.8512
O1	-0.0116	81.82	90.91	86.36	0.9174
O2	-0.0079	81.82	81.82	81.82	0.8760

4. Discussion and Conclusions

In this pilot study, we have studied the EEG background activity of 11 AD patients and 11 age-matched, elderly control subjects by means of the *MSE*, which assesses the signal complexity estimating the regularity of coarse-grained sequences on different time scales. The *MSE* is a suitable method to analyse physiological signals, since it can be applied to relatively short, noisy time series, irrespective of whether their origin is stochastic or deterministic (Costa *et al* 2005). The *MSE* curves can be used to compare qualitatively the signal complexity of different time series (Costa *et al* 2005). Particularly, a monotonic decrease of the *SampEn* values with τ indicates that the analysed signal is a completely independent random sequence, since it contains information only on the smallest time scale (Costa *et al* 2005). In contrast to this relatively simple *MSE* profile that characterizes randomness, the EEG *MSE* curves can be divided into two different parts. The first one corresponds to the small time scales, and it is characterized by a steep increasing slope. On the other hand, in the second part of the *MSE* profiles the slope is much smoother, and it can be either increasing or decreasing. Thus, the EEG *MSE* profiles suggest that the EEG do not have a completely stochastic origin (Costa *et al* 2005). Moreover, the *MSE* analysis revealed the EEG complex structure and showed the presence of long-range correlations (Costa *et al* 2005), which have been associated with complex physiological systems (Goldberger *et al* 2002).

The *MSE* analysis reveals that the AD patients usually have lower *SampEn* values on the small and medium time scales at most electrodes of the 10-20 system. If most scales present higher *SampEn* values for one signal than for another, the former is considered more complex than the latter (Costa *et al* 2005). Therefore, we can infer that brain activity is less complex in AD patients than in control subjects. This result agrees with other studies that revealed less complexity (Besthorn *et al* 1995, Jelles *et al* 1999, Jeong *et al* 1998, 2001a, Pritchard *et al* 1994, Stam *et al* 1995) or less irregularity (Abásolo *et al* 2005, 2006a, b) in the EEG recordings of AD patients than in control subjects. For instance, Besthorn *et al* (1995) found significant lower D_2 values in AD patients than control subjects. Besides, those values were correlated with the severity of AD, and an accuracy of 70% in the classification of subjects was reached. In Pritchard *et al* (1994) it was proven that the addition of D_2 and a neural network classification algorithm to the traditional linear methods could improve the classification accuracy of AD patients against control subjects up to 92%. Similarly to D_2, L_1 could be also considered as a kind of complexity measure, since it estimates the flexibility of a system to reach different states from almost identical initial states (Wolf *et al* 1985). In this sense, L_1 is interpreted as a measure of the brain flexibility to process information. Several studies have verified that the difficulties to process information of AD patients produce lower L_1 values than control subjects (Jeong *et al* 1998, 2001a, Stam *et al* 1995). These kinds of complexity reduction have been related to a drop of the subject adaptive capabilities (Goldberger *et al* 2002).

The aforementioned increased regularity on nearly all scales may have their origin in a widespread complexity loss in the brain of AD patients (Jeong 2004). Although such complexity reduction seems to be associated with the AD deficiencies in information processing, its physiological origin is not clear. The main reasons for the lower complexity might be an extensive neuronal death, a general effect of neurotransmitter deficiency or a decrease in the connectivity of local neural networks due to nerve cell death (Jelles *et al* 1999, Jeong 2004, Tononi *et al* 1998). Whatever the physiological cause is, the impairments in information processing of AD patients could be produced by either an inactivation of previously active neural networks or a decline in the dynamical responsivity to outer stimuli (Jeong 2004).

The slope of the *MSE* profiles on the small time scales ($\tau \leq 5$) revealed no significant group differences. We can infer that the EEG background activity of control subjects and AD patients evolves in a very similar way on these time scales. However, we have found important differences in the *MSE* profiles on the larger time scales. In fact, the slopes of the *MSE* profiles of both groups for $\tau \geq 6$ are significantly different (p-value < 0.01) at ten electrodes located in the left frontal (F3 and F7), frontopolar (Fp1 and Fp2) and posterior brain regions (T5, T6, P3, P4, O1 and O2). The main discrepancy between both groups was that the irregularity of the coarse-grained sequences tended to decrease for the control group whereas it remained almost

constant or slightly increased for AD patients. It shows that the correlation in the EEG background activity of the control subjects weakens on the largest time scales (Costa *et al* 2005). This finding suggests that it might be more difficult to predict the EEG background activity in control subjects than in AD patients, which agree with the steeper slopes of the Auto-Mutual Information found by Jeong *et al* (2001b) in control subjects than in AD patients.

We used ROC curves in order to assess the ability of the slope on the large time scales to assist in clinical classification of AD patients against control subjects. Whereas the minimum accuracy of the ROC curves was obtained at electrode F7 (77.27%), the highest accuracy and larger area under the ROC curves were found at electrode Fp1, in which the accuracy was higher than 90% (90.91%). Accuracy values close to 90% were also obtained at electrodes Fp2, T5, P3 and O1 (86.36%). Nevertheless, these accuracy results should be taken with caution because of the small sample size.

Previous studies had observed that the severity of the AD was correlated with the D_2 values (Besthorn *et al* 1995) and with the decrease of the Auto-Mutual Information function (Jeong *et al* 2001b) in AD patients. However, we found no correlation between the AD patients' MMSE scores and the average slope values of the *MSE* profiles for large time scales. A possible explanation for this fact may be that Besthorn *et al* (1995) analysed EEG signals from a larger database than ours (50 AD patients). Moreover, the AD group studied by Jeong *et* al (2001b) was also more severely demented (MMSE = 9.4 ± 3.43 points, mean ± SD) than the AD patients analysed in this study.

Our study has some limitations which need to be paid attention on. First of all, the sample size was small. In this study, we set a strict significance level ($\alpha = 0.01$) to minimize the type I error (the error of statistically rejecting a true null hypothesis). As a result, this may have increased the probability of a type II error (the error of statistically accepting a false null hypothesis). Moreover, the probability of a type II error may be taken into consideration due to the wider confidence interval associated with the small sample size. Therefore, although the results seem to indicate that the *MSE* could help in the diagnosis of AD, the study should be extended on a much larger patient population before it could be accepted as a diagnostic tool with clinical value. Besides, other physiological and pathological states of the brain should be analysed with *MSE* in order to know whether our findings are specific to AD or not, since other researches have found an increase of regularity in other diseases and states of the brain, including sleep (Burioka *et al* 2003), anaesthesia (Zhang and Roy 2001, Ferenets *et al* 2006), Parkinson's disease (Stam *et al* 1995) and epilepsy (Hornero *et al* 1999). The ageing process can also produce a wide-ranging loss of physiological complexity (Kyriazis 2003). Thus, it is possible that some of these diseases or states may produce *MSE* profiles similar to those from AD.

Despite these drawbacks, the *MSE* analysis has important advantages over other traditionally used non-linear analysis methods, such as D_2 and L_1: the *MSE* can be applied to relatively noisy, short physiological time series, and it is model-independent (Costa *et al* 2005). Other non-linear analysis methods that have recently been applied to EEG signals have also these desirable properties (e.g.: *ApEn*, *SampEn* or *LZ* complexity). Nevertheless, the *MSE* analysis may be a more suitable method to analyse the EEG recordings due to some of its specific characteristics. On the one hand, *ApEn* and *SampEn* are regularity estimators derived from the entropy analysis of the signals (Costa *et al* 2005). They are based on evaluating the appearance of repetitive patterns in the time series (Pincus 1991, Richman and Moorman 2000). Particularly, *ApEn* is derived from the Kolmogorov-Sinai entropy in the sense that the limits $r \to 0$, $N \to \infty$ and $m \to \infty$ can be relaxed (Ferenets *et al* 2006). On the other hand, *LZ* complexity is a complexity measure in the Kolmogorov's sense. It is a non-parametric method which measures the number of different substrings and the rate of their recurrence along the original signals (Lempel and Ziv 1976). However, *LZ* complexity characterizes the randomness of a system, and not its complexity in a strict sense (Tononi *et al* 1998), as noted by Lempel and Ziv (1976) in their original study. Contrary to *ApEn*, *SampEn* or *LZ* complexity, the *MSE* fulfils the criterion that has been adopted in this study for a real complexity measure. The *MSE* distinguishes both completely random and completely ordered signals from real complex ones

(Costa *et al* 2005). Moreover, the *MSE* is based on the idea that physiologic systems are governed by mechanisms that operate across multiple time scales. Therefore, the *MSE* analysis shows features of the signal that simultaneously depend on several time scales. Thus, the real underlying dynamics of the generating system can be revealed (Costa *et al* 2005), providing a useful insight into the signal structure. In addition, the importance of the external measure white noise is reduced as deeper time scales are inspected, due to the averaging process employed in the calculation of the coarse-grained sequences. Furthermore, our results suggest that the *MSE* analysis of EEG is coherent with the theory of complexity loss in disease (Goldberger *et al* 2002), which relates disease to less complex biomedical signals. Due to these specific characteristics of the *MSE*, it may be more helpful in the diagnosis of AD than other non-linear analysis techniques. In the following lines we compare the results of the current study with several studies which used the *ApEn* (Abásolo 2006), *SampEn* (Abásolo *et al* 2006a) and *LZ* complexity (Abásolo *et al* 2006b) to distinguish AD patients from control subjects. The comparison is straightforward since the same data set was used in all the analyses. A summary of the accuracies and area under the ROC curve values obtained with *ApEn*, *SampEn* and *LZ* complexity in those studies is shown in table 4.

Table 4. Summary of the accuracy and area under the ROC curve values obtained applying *ApEn*, *SampEn* and *LZ* complexity to the same data set used in this study. Only the electrodes where significant differences between control subjects and AD patients were found (p-value < 0.01) are shown.

Non-linear analysis method	Electrode	Sensitivity (%)	Specificity (%)	Accuracy (%)	Area under the ROC curve
ApEn with m = 1 and r = 0.25SD (Abásolo 2006)	P3	72.73	81.82	77.27	0.8595
	P4	63.64	81.82	72.73	0.8264
	O1	81.82	72.73	77.27	0.8595
	O2	90.91	63.64	77.27	0.7769
SampEn with m = 1 and r = 0.25SD (Abásolo *et al* 2006a)	P3	72.73	81.82	77.27	0.8512
	P4	63.64	90.91	77.27	0.8347
	O1	81.82	72.73	77.27	0.8595
	O2	90.91	63.64	77.27	0.7769
LZ complexity with a three symbol conversion (Abásolo *et al* 2006b)	T5	72.73	72.73	72.73	0.8017
	P3	81.82	81.82	81.82	0.8926
	P4	72.73	90.91	81.82	0.8430
	O1	90.91	72.73	81.82	0.8512

The comparison of these results should be taken with caution due to the small database size. However, comparing tables 3 and 4, we can realize that the *MSE* analysis provided statistically significant differences in more electrodes (ten electrodes of the 10-20 system) than *LZ* complexity, *ApEn* or *SampEn* did (4 electrodes in all cases). Moreover, the accuracy and area under the ROC curve values found using the *MSE* analysis were usually higher than the corresponding values of the other methods. For example, the *MSE* was able to differentiate control subjects from AD patients with accuracies higher than 85 % at five electrodes (Fp1, Fp2, T5, P3 and O1). In contrast, none of the other methods provided accuracy values over 85 %. In addition, the areas under the ROC curves were larger than 0.900 for the *MSE* analysis at electrodes Fp1, T5, T6, P3 and O1, whereas values this high were not reached with *ApEn*, *SampEn* and *LZ* complexity. Furthermore, the improvement in the accuracy values of the *MSE* analysis is due to an improvement in both sensitivity and specificity parameters. Table 3 shows that in seven of the ten electrodes both sensitivity and specificity values were higher than 80 %. This improvement in the classification rate could be due to simultaneous inspection of several time scales that the *MSE* analysis performs.

To sum up, we found significant differences between AD patients and control subjects on the large time scales at ten electrodes (F3, F7, Fp1, Fp2, T5, T6, P3, P4, O1 and O2). Although this pilot study is only a first step in the inspection of the EEG with *MSE*, and it has the reported

limitations, our results suggest that AD is characterized not only by changes in the brain activity on the shortest time scale, but also by an abnormal behaviour on deeper time scales. However, the *MSE* analysis of the EEG cannot yet be applied in the diagnosis of AD and further studies with a larger sample size must be carried out to confirm our results.

Acknowledgements

This study was partially supported by the grant project from "Consejería de Educación de la Junta de Castilla y León" VA108A06 and the "Ministerio de Educación y Ciencia" and FEDER grant MTM 2005-08519-C02-01. The authors are thankful for the useful comments of the referees.

References

Abásolo D 2006 Análisis no Lineal de la Actividad Base del Electroencefalograma. Aplicación a la Enfermedad de Alzheimer *PhD Thesis* University of Valladolid, Spain

Abásolo D, Hornero R, Espino P, Álvarez D, and Poza J 2006a Entropy analysis of the EEG background activity in Alzheimer's disease patients *Physiol. Meas.* **27** 241–53

Abásolo D, Hornero R, Espino P, Poza J, Sánchez C I and de la Rosa R 2005 Analysis of regularity in the EEG background activity of Alzheimer's disease patients with Approximate Entropy *Clin. Neurophysiol.* **116** 1826–34

Abásolo D, Hornero R, Gómez C, García M and López M 2006b Analysis of EEG background activity in Alzheimer's disease patients with Lempel-Ziv complexity and central tendency measure *Med. Eng. Phys.* **28** 315–22

Babloyantz A and Destexhe A 1988 The Creutzfeldt-Jakob disease in the hierarchy of chaotic attractors *From Chemical to Biological Organization* ed M Markus *et al* (Berlin: Springer-Verlag) pp 307–16

Besthorn C, Sattel H, Geiger-Kabisch C, Zerfass R and Förstl H 1995 Parameters of EEG dimensional complexity in Alzheimer's disease *Electroencephalogr. Clin. Neurophysiol.* **95** 84–89

Bhattacharya J, Edwards J, Mamelak A N and Schuman E M 2005 Long-range temporal correlations in the spontaneous spiking of neurons in the hippocampal-amygdala complex of humans *Neuroscience* **131** 547–55

Bird T D 2001 Alzheimer's disease and other primary dementias *Harrison's Principles of Internal Medicine* ed E Braunwald *et al* (New York: The McGraw-Hill Companies Inc) pp 2391–9

Burioka N, Cornélissen G, Halberg F, Kaplan D T, Suyama H, Sako T and Shimizu E 2003 Approximate entropy of human respiratory movement during eye-closed waking and different sleep stages *Chest* **123** 80–6

Costa M, Goldberger A L and Peng C K 2002 Multiscale entropy analysis of complex physiologic time series *Phys. Rev. Lett.* **89** 068102

Costa M, Goldberger A L and Peng C K 2004 Reply to (Nikulin and Brismar 2004) *Phys. Rev. Lett.* **92** 089804

Costa M, Goldberger A L and Peng C K 2005 Multiscale entropy analysis of biological signals *Phys. Rev.* E **71** 021906

Eckmann J P and Ruelle D 1992 Fundamental limitations for estimating dimensions and Lyapunov exponents in dynamical systems *Physica* D **56** 185–7

Ferenets R, Lipping T, Anier A, Jäntti V, Melto S and Hovilehto S 2006 Comparison of entropy and complexity measures for the assessment of depth of sedation *IEEE Trans. Biomed. Eng.* **53** 1067–77

Ferrario M, Signorini M G, Magines G and Cerutti S 2006 Comparison of entropy-based regularity estimators: application to the fetal heart rate signal for the identification of fetal distress *IEEE Trans. Biomed. Eng.* **53** 119–25

Folstein M F, Folstein S E and McHugh P R 1975 Mini-mental state. A practical method for grading the cognitive state of patients for the clinician *J. Psychiatr. Res.* **12** 189–98

Goldberger A L, Peng C K and Lipsitz L A 2002 What is physiologic complexity and how does it change with aging and disease? *Neurobiol. Aging* **23** 23–6

Grassberger P and Procaccia I 1983a Measuring the strangeness of strange attractors *Physica* D **9** 189–208

Grassberger P and Procaccia I 1983b Characterization of strange attractors *Phys. Rev. Lett.* **50** 346–9

Hornero R, Aboy M, Abásolo D, McNames J and Goldstein B 2005 Interpretation of approximate entropy: analysis of intracranial pressure approximate entropy during acute intracranial hypertension *IEEE Trans. Biomed. Eng.* **52** 1671–80

Hornero R, Espino P, Alonso A and López M 1999 Estimating complexity from EEG background activity of epileptic patients *IEEE Eng. Med. Biol. Mag.* **18** 73–9

Jelles B, van Birgelen J H, Slaets J P J, Hekster R E M, Jonkman E J and Stam C J 1999 Decrease of non-linear structure in the EEG of Alzheimer patients compared to healthy controls *Clin. Neurophysiol.* **110** 1159–67

Jeong J 2004 EEG dynamics in patients with Alzheimer's disease *Clin. Neurophysiol.* **115** 1490–505

Jeong J, Chae J H, Kim S Y and Han S H 2001a Nonlinear dynamic analysis of the EEG in patients with Alzheimer's disease and vascular dementia *J. Clin. Neurophysiol.* **18** 58–67

Jeong J, Gore J C, Peterson B S 2001b Mutual information analysis of the EEG in patients with Alzheimer's disease *Clin. Neurophysiol.* **112** 827−35

Jeong J, Kim S J and Han S H 1998 Non-linear dynamical analysis of the EEG in Alzheimer's disease with optimal embedding dimension *Electroencephalogr. Clin. Neurophysiol.* **106** 220–8

Kyriazis M 2003 Practical applications of chaos theory to the modulation of human ageing: nature prefers chaos to regularity *Biogerontology* **4** 75–90

Lahiri D K, Farlow M R, Greig N H and Sambamurti K 2002 Current drugs targets for Alzheimer's disease treatment *Drug. Dev. Res.* **56** 267–81

Lake D E, Richman J S, Griffin M P and Moorman J R 2002 Sample entropy analysis of neonatal heart rate variability *Am. J. Physiol.* (*Regul. Integr. Comp. Physiol.*) **283** R789–97

Lempel A, Ziv J 1976 On the complexity of finite sequences *IEEE Trans. Inform. Theory* **22** 75–81

López-Ruiz R, Mancini H L and Calbet X 1995 A statistical measure of complexity *Phys. Lett.* A **209** 321–6

Markand O N 1990 Organic brain syndromes and dementias *Current Practice of Clinical Electroencephalography* ed D D Daly and T A Pedley (New York: Raven Press) pp 401–23

Nikulin V V, Brismar T 2004 Comment on "Multiscale Entropy Analysis of Complex Physiologic Time Series" *Phys. Rev. Lett.* **92** 089803

Pincus S M 1991 Approximate entropy as a measure of system complexity *Proc. Natl. Acad. Sci. USA* **88** 2297–2301

Pincus S M 2001 Assessing serial irregularity and its implications for health *Ann. NY Acad. Sci.* **954** 245–67

Pritchard W S, Duke D W, Coburn K L, Moore N C, Tucker K A, Jann M W and Hostetler R M 1994 EEG-based neural-net predictive classification of Alzheimer's disease versus control subjects is augmented by non-linear EEG measures *Electroencephalogr. Clin. Neurophysiol.* **91** 118–30

Radhakrishnan N and Gangadhar B N 1998 Estimating regularity in epileptic seizure time-series data *IEEE Eng. Med. Biol.* **17** 89–94

Richman J S and Moorman J R 2000 Physiological time-series analysis using approximate entropy and sample entropy *Am. J. Physiol.* (*Heart Circ. Physiol.*) **274** H2039–49

Stam C J, Jelles B, Achtereekte H A M, Rombouts S A R B, Slaets J P J and Keunen R W M 1995 Investigation of EEG non-linearity in dementia and Parkinson's disease *Electroencephalogr. Clin. Neurophysiol.* **95** 309–17

Tononi G, Edelman G M and Sporns O 1998 Complexity and coherency: integrating information in the brain *Trends Cogn. Sci.* **2** 474–84

Tononi G, Sporns O and Edelman G M 1994 A measure for brain complexity: Relating functional segregation and integration in the nervous system *Proc. Natl. Acad. Sci. USA* **91** 5033–7

Wolf A, Swift J B, Swinney H L and Vastano J A 1985 Determining Lyapunov exponents from a time-series *Physica* D **16** 285–317

Zhang X S and Roy R J 2001 Derived fuzzy knowledge model for estimating the depth of anesthesia *IEEE Trans. Biomed. Eng.* **48** 312–23

Zhang X S, Roy R J and Jensen EW 2001 EEG complexity as a measure of depth of anesthesia for patients *IEEE Trans. Biomed. Eng.* **48** 1424–33

Zweig M H and Campbell G 1993 Receiver-Operating Characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine *Clin. Chem.* **39** 561–77