Analysis of regularity in the EEG background activity of Alzheimer's disease patients with Approximate Entropy

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Abstract

Objective: The aim of this study was to analyse the regularity of the EEG background activity of Alzheimer's disease (AD) patients to test the hypothesis that the irregularity of the AD patients' EEG is lower than that of age-matched controls.

Methods: We recorded the EEG from 19 scalp electrodes in 10 AD patients and 8 age-matched controls and estimated the Approximate Entropy (*ApEn*). *ApEn* is a non-linear statistic that can be used to quantify the irregularity of a time series. Larger values correspond to more complexity or irregularity. A spectral analysis was also performed.

Results: *ApEn* was significantly lower in the AD patients at electrodes P3 and P4 ($p < 0.01$), indicating a decrease of irregularity. We obtained 70% sensitivity and 100% specificity at P3, and 80% sensitivity and 75% specificity at P4. Results seemed to be complementary to spectral analysis.

Conclusions: The decreased irregularity found in the EEG of AD patients in the parietal region leads us to think that EEG analysis with *ApEn* could be a useful tool to increase our insight into brain dysfunction in AD. However, caution should be applied due to the small sample size.

Significance: This article represents a first step in demonstrating the feasibility of *ApEn* for recognition of EEG changes in AD.

Keywords: Alzheimer's disease; EEG; Approximate Entropy

1. Introduction

Non-linearity as a necessary condition for chaotic behaviour is present in many dynamical systems found in nature. For a neuronal network such as the brain, non-linearity 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. For these reasons, the electroencephalogram (EEG) appears to be an appropriate area for non-linear time series analysis (Kantz and Schreiber, 1997).

Owing to the highly complicated structure of the brain is questionable whether EEG time series, particularly those of short duration, can carry enough information to reveal dynamical properties of the underlying system, i.e. the brain (Andrzejak et al., 2001). Many studies are known in which non-linear time series analysis techniques were applied to different kinds of EEGs from humans, such as recordings from healthy volunteers at rest (Stam et al., 1999), sleep (Babloyantz et al., 1985), during periods of cognitive activity (Theiler and Rapp, 1996), or from patients with acute ischemic stroke (Hwa and Ferree, 2002) or with diseases like Alzheimer's (Stam et al., 1995; Jelles et al., 1999), Parkinson's (Pezard et al., 2001), Creutzfeldt-Jakob (Babloyantz and Destexhe, 1988), epilepsy (Hornero et al., 1999), depression (Nandrino et al., 1994) and schizophrenia (Fell et al., 1995) in comparison with control subjects.

Interpretations of results ranged from "evidence for chaotic attractors" underlying sleep recordings (Babloyantz et al., 1985) to the conclusion that EEG data of healthy volunteers "may be more appropriately modelled by linearly filtered noise" (Theiler and Rapp, 1996). Besides the aim of finding a certain dynamical model for the EEG, non-linear studies of the brain have proven to be very useful in making relative comparisons of different physiological states (Theiler and Rapp, 1996; Jeong, 2004).

Alzheimer's disease (AD) is considered to be the main cause of dementia in western countries (Bird, 2001). Clinically, this degenerative neurological disease manifests as a slowly progressive impairment of mental functions whose course lasts several years prior to death. The brain of AD patients shows a diffuse atrophy of the cortex and, microscopically, there exist neuritic plaques containing amyloid A β , neurofibrillary tangles and deposits of amyloid in the walls of the brain arteries. 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. In these patients, the EEG shows generalized changes with a diffuse slowing of the background activity (Markand, 1990), although in the early stages of the disease the EEG may exhibit normal frequencies.

There are several research works of the EEG in AD patients with non-linear methods. For instance, Pijnenburg et al. (2004) have studied the EEG synchronization likelihood in AD during a working memory task and have found a decrease of beta band synchronization both in a resting condition and during a working memory task. Non-linear forecasting and entropy maps have been used to characterize drug effects on brain dynamics in AD (Pezard et al., 1998) and mutual information analysis to assess information transmission between different cortical areas in AD (Jeong et al., 2001b). However, the most frequently used non-linear method is the correlation dimension (D_2), a measure of dimensional complexity of the underlying system (Grassberger and Procaccia, 1983a). Results showed that AD patients had lower D_2 values than controls

(Stam et al., 1995; Jeong et al., 1998, 2001a). Furthermore, Besthorn et al. (1995) showed that a lower D_2 was correlated with increased severity of dementia and also found that this method correctly classified AD patients and controls with an accuracy of 70% (Besthorn et al., 1997).

Nevertheless, there are some drawbacks in D_2 . The amount of data required for meaningful results is beyond the experimental possibilities for physiological data (Eckmann and Ruelle, 1992) and the Grassberger and Procaccia algorithm or its modifications used to estimate the 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 apply other non-linear methods to study the EEG background activity.

One possible 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. Kolmogorov-Sinai entropy (K-S entropy), developed by Kolmogorov and expanded upon by Sinai, allows classifying deterministic dynamical systems by rate of information generation (Kolmogorov, 1958). Unfortunately, K-S entropy was not developed for statistical applications and diverges to a value of infinity when the signal is contaminated by the slightest noise. A practical solution to this problem has been put forward using a recently developed family of statistics named Approximate Entropy (*ApEn*) (Pincus, 1991). Although there are many other entropy estimators, several properties of *ApEn* facilitate its utility for empirical time series analysis of the sort of EEGs: *ApEn* is nearly unaffected by noise below a *de facto* specified filter level (r), it can be applied to time series of 50 or more points with good reproducibility; it is finite for stochastic, noisy deterministic and composite processes, and increasing values of *ApEn* correspond to more irregularity or to increasing complexity in the time series (Pincus 2001).

Preliminary evidence suggests that applied to EEGs *ApEn* is predictive of epileptic seizures (Radhakrishnan and Gangadhar, 1998). It has also been used to discriminate atypical EEGs (Bruhn et al., 2000) and to quantify the depth of anaesthesia (Zhang and Roy, 2001). Moreover, it has been showed that *ApEn* follows closely the results obtained from spectral entropy extracting features from EEG and respiratory recordings of a patient during Cheyne-Stokes respiration, with apparently higher sensitivity and reduced error (Rezek and Roberts, 1998).

This preliminary study was undertaken to examine the EEG background activity in AD with *ApEn*. We wanted to test the hypothesis that the irregularity (or complexity) of the AD patients' EEG is lower than that of age-matched controls, hence indicating an abnormal type of dynamics in this group. As it is known that non-linear measures are influenced by linear measures, we also performed a spectral analysis to compare *ApEn* results with the slowing of the EEG rhythms usually found in AD (Markand, 1990). We wanted to test if *ApEn* could reveal characteristics of the signal that might remain undetected with linear (spectral) analysis.

2. Methods

2.1. Selection of patients and controls

We studied 10 patients (4 men and 6 women; age = 74.8 ± 3.9 years, mean $\pm$ standard deviation SD) fulfilling the criteria of probable AD. The patients 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). Five patients had a MMSE score of less than 12 points, indicating a severe degree of dementia. The mean MMSE score for the patients was 12.6 ± 5.9 (Mean $\pm$ SD). Two subjects were receiving lorazepam. With therapeutic doses, benzodiazepines may enhance beta activity, although no prominent rapid rhythms were observed in the visual examination of these two subjects' EEGs. None of the other patients used medication that could be expected to influence the EEG.

The control group consisted of 8 age-matched, elderly healthy cognitively normal controls without past or present neurological disorders (6 men and 2 women; age = 74.9 ± 5.9 years, mean $\pm$ SD). The MMSE score value for all control subjects was 30. The main characteristics of the control subjects and patients with AD (age, sex and MMSE scores for both groups and visual analysis of the patients' EEGs) are summarized in Table 1.

 Insert Table 1 around here

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. An EEG was recorded from all patients and controls.

2.2. EEG recording

The EEGs were recorded from the 19 scalp loci of the international 10-20 system (channels Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz and Pz), with all electrodes referenced to the chin. With the subjects in a relaxed state, awake and with closed eyes, more than five minutes of data were recorded from each subject using a Profile Study Room 2.3.411 EEG equipment (Oxford Instruments). EEG data were first processed with a low-pass hardware filter at 100 Hz. Then they were sampled at 256 Hz, with a 12-bit A-to-D precision, and processed with a high-pass filter at 70 Hz. Recordings were made under the eyes-closed condition in order to obtain as many artefact-free EEG data as possible.

Each EEG record was judged by visual inspection to be free from electrooculographic and movement artefacts and to contain minimal electromyographic (EMG) activity. Besides, EEGs were organized in epochs of 5 seconds (1280 points) that began when the recording was stable (i.e., the noisy parts at the beginning of the recording were discarded). All data 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 *ApEn* and relative power calculations. An average number of 30.0 ± 13.0 artefact-free epochs (Mean $\pm$ SD) were selected from each electrode and each subject and copied as ASCII files for off-line analysis on a personal computer.

2.3. Approximate entropy (*ApEn*)

ApEn was introduced as a quantification of regularity in sequences and time series data, initially motivated by applications to relatively short, noisy data sets (Pincus, 1991). It is scale invariant and model independent, evaluates both dominant

and subordinated patterns in data, and discriminates series for which clear feature recognition is difficult. Notably, it detects changes in underlying episodic behaviour not reflected in peak occurrences or amplitudes (Pincus and Keefe, 1992). *ApEn* assigns a non-negative number to a time series, with larger values corresponding to more complexity or irregularity in the data (Pincus, 2001). Formally, given N data points from a time series $\{x(n)\}=x(1), x(2), \dots, x(N)$, two input parameters m and r , must be fixed to compute *ApEn*, denoted precisely by $ApEn(m, r, N)$. To estimate *ApEn*, first form vector sequences $X(1) \dots X(N-m+1)$, defined by $X(i)=[x(i), x(i+1), \dots, x(i+m-1)]$, $i=1 \sim N-m+1$. These vectors represent m consecutive x values, commencing with the i th point. Define the distance between $X(i)$ and $X(j)$, $d[X(i), X(j)]$, as the maximum absolute difference between their respective scalar components. For a given $X(i)$, count the number of j ($j=1 \sim N-m+1$, $j \neq i$) so that $d[X(i), X(j)] \leq r$, denoted as $N^m(i)$. Then, for $i=1 \sim N-m+1$, calculate $C_r^m(i)=N^m(i)/(N-m+1)$. The $C_r^m(i)$ values measure within a tolerance r the regularity, or frequency, of patterns similar to a given one of window length m . Next, obtain $\phi^m(r)$ as the average value of $\ln C_r^m(i)$. $\phi^m(r)$ portrays the average frequency that all the m -point patterns in the sequence remain close to each other. We define *ApEn* by (Pincus, 2001):

$$ApEn(m, r, N) = \phi^m(r) - \phi^{m+1}(r) \quad (1)$$

Briefly, *ApEn* 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. Comparisons between time series segments can only be made with the same values of m and r (Pincus, 2001).

Because of the non-linear character of EEG signals, *ApEn* can be used as a powerful tool in the study of the EEG background activity of AD patients. Although m and r are critical in determining the outcome of *ApEn*, no guidelines exist for optimising 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). However, there are penalties for criteria that are too relaxed (Pincus, 1991). Pincus (2001) has suggested to estimate *ApEn* with parameter values of $m=1$, $m=2$ and $r=0.1, 0.15, 0.2$ and 0.25 times the SD of the original data sequence $\{x(n)\}$. Normalizing r in this manner gives *ApEn* a translation and scale invariance, in that it remains unchanged under uniform process magnification, reduction, or constant shift to higher or lower values (Pincus, 2001). Moreover, several studies (Pincus, 1991; Pincus and Keefe, 1992) have demonstrated that these input parameters produce good statistical reproducibility for *ApEn* for time series of length $N \geq 60$, as considered herein. For this pilot study, *ApEn* was estimated with $m=1$ and $r=0.2$ times the SD of the original data sequence. Calculation of *ApEn* from the EEG signals was done with software developed with MATLAB[®].

2.4. Spectral analysis

The power spectral density for each signal was estimated as the Fourier transform of the autocorrelation function. The powers were integrated in the following frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–40 Hz). The relative power for each frequency band was computed by dividing the integrated value by the total power in the 0.5 to 40 Hz frequency band.

3. Results

ApEn was estimated for channels Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5 and T6 with $m=1$ and $r=0.2$ times the SD of the original data sequence. The results have been averaged based on all the artefact-free 5 second epochs ($N=1280$ points) within the five-minute period of EEG recordings. The *ApEn* values (Mean $\pm$ SD) for the AD patients and control subjects and the p -values of the one-way ANOVA test performed to examine the differences between both groups are summarized in Table 2.

Insert Table 2 around here

It can be seen that AD patients had lower *ApEn* values at 14 electrodes, with significant differences between both groups at electrodes P3 ($p=0.002<0.01$) and P4 ($p=0.005<0.01$). These results suggest that EEG activity of AD patients is more regular (less complex) in the parietal region than in a normal brain. AD patients had slightly higher *ApEn* values at 2 electrodes, F7 and T4, although the differences were not significant ($p=0.747$ and $p=0.931$, respectively). Further inspection of the results showed a certain rhythmical activity in some of the control subjects' EEG epochs at those electrodes, which led to the estimation of reduced *ApEn* values.

To quantify the variability of *ApEn* results we have calculated the intersubject coefficients of variation (the SD divided by the mean). Results showed that the intersubject variability of *ApEn* was greater for AD patients than for control subjects at electrodes C3, C4, Fp1, T4, T5, T6, P3, P4, O1 and O2. By comparison, the intrasubject variability of *ApEn* results was greater for AD patients than for control subjects at all electrodes. The intersubject and mean intrasubject ($\pm$ SD) coefficients of variation of *ApEn* are summarized in Table 3.

Insert Table 3 around here

Finally, we evaluated the ability of *ApEn* to discriminate AD patients from control subjects at electrodes P3 and P4 using Receiver Operating Characteristic (ROC) plots (Zweig and Campbell, 1993). We used a computer program developed with Matlab[®] that automatically selected different thresholds or cut-off points (*ApEn* values) and calculated the sensitivity/specificity pair for each one of them. Sensitivity – the true positive rate – is the proportion of patients with a diagnosis of AD who test positive (*ApEn* value lower than the cut-off point), whereas specificity – the true negative rate – represents the percentage of healthy subjects correctly recognized (*ApEn* value higher than the cut-off point). Accuracy is a related measure that quantifies the number of subjects (AD patients and control subjects) accurately classified. The program selected the optimum threshold as the cut-off point in which the highest accuracy (minimal false negative and false positive results) is obtained. It was determined graphically from the ROC curve as the closest value to the left top point (100% sensitivity, 100% specificity).

We obtained 70% sensitivity and 100% specificity at P3 (area under the ROC curve: 0.887; optimum threshold: 0.8714) and 80% sensitivity and 75% specificity at P4 (area under the ROC curve: 0.862; optimum threshold: 0.9409). Figure 1 shows the ROC curves for both electrodes.

Insert figure 1 around here

A rough guide 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 0.90, 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 at electrodes P3 and P4 can be considered good.

The relative power in the delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–40 Hz) frequency bands was calculated in order to test if what *ApEn* detects is anything else but slowing. The relative power values (Mean $\pm$ SD) are shown in Table 4. Values for the 30-40 Hz band (the fraction of the gamma band included in the filtered EEG epochs we have studied) are not included as they were too small and did not show significant differences between AD patients and control subjects.

Insert Table 4 around here

The spectral analysis showed an increase of the relative power values in the delta band in AD patients, with significant differences between both groups at P4, O2 and T4 ($p < 0.01$). The values were also higher in the theta band for AD patients than for control subjects, although the differences were not relevant ($p > 0.01$). A decrease of the relative power in the alpha band of AD patients was also found, with significant differences at electrodes T3 and T4 ($p < 0.01$). On the other hand, the decrease of the relative power in the AD patients' beta band was not significant.

4. Discussion

In this pilot study we have analysed the EEG background activity of 8 control subjects and 10 patients with AD by means of *ApEn*, a non-linear method that quantifies the regularity (or complexity) of time series. *ApEn* can give a robust entropy estimate from short and noisy data sets and increasing values correspond to more irregularity or to increasing complexity in the time series (Pincus, 2001).

We have found that AD patients have significantly lower *ApEn* values than control subjects at electrodes 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 region. This confirms findings associated with the fact that a diffuse slowing of the background activity may be found in the EEGs of patients with AD (Markand, 1990) and that the dynamic processes underlying the EEG recording are less complex for AD patients than for normal subjects (Besthorn et al., 1995, 1997; Jeong et al., 1998; Jelles et al., 1999; Jeong et al., 2001a). This reduction of irregularity could be explained by a

decrease of dynamical complexity of part of the brain in AD patients. However, the pathophysiological implications of the decreased EEG irregularity or complexity in AD patients are not clear (Jeong, 2004). Among others, three mechanisms can be responsible for this decrease of complexity: 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).

$ApEn(m=1, r=0.2)$ reflects the rate of new pattern generation when the dimension m decreases from 2 to 1 (Fusheng et al., 2001). A larger value of $ApEn$ means that the chance of new pattern generation is greater, so the sequence is more irregular or complex, and vice versa. Given that EEG patterns reflect cortical activity (information processing) of the brain, the reduced $ApEn$ in AD patients' EEG suggests the deficient information processing of the cortex due to the inactivation of previously active networks (Jeong, 2004). We compared our results by means of sensitivity, specificity and accuracy with a selected threshold to improve the sensitivity/specificity pair according to ROC plots (Zweig and Campbell, 1993). The highest specificity was obtained at electrode P3 (100%), while the sensitivity was better at P4 (80%). The best accuracy was obtained at electrode P3 (83.3%).

It should be noted that the intrasubject and intersubject coefficients of variation of $ApEn$ in our study were greater than the reported values in other research work (Burioka et al., 2003). This can be due to the use of a different epoch size. Burioka et al. (2003) analysed 20 second epochs, while we have used 5 second artefact-free EEG segments. We chose that length for two reasons: (i) to maximize the number of artefact-free epochs and (ii) to obtain a more detailed insight of the EEG dynamics (i.e. the estimation of $ApEn$ with smaller epochs from the same EEG recording could help to detect characteristics that might not be noticed with larger epoch sizes). However, this might also be the reason for the greater $ApEn$ variability reported in our study. Moreover, Burioka et al. (2003) analysed EEG data just from one position (C3), while we have studied data from 16 electrodes.

In order to compare the $ApEn$ results with more conventional EEG measures, we performed a spectral analysis of the data. As expected, it showed the slowing of the EEG in AD patients, 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. With the exception of the increase of delta power at channel P4, the significant differences between both groups were obtained at different electrodes than with $ApEn$. According to Pincus (2001), $ApEn$ provides effective discriminatory capability in instances in which the spectral analysis exhibit minimal distinctions. Thus, our results suggest that this entropy estimator might be complementary to spectral and autocorrelation analyses. However, due to the preliminary nature of the study and small sample size, a possible association should be investigated with a larger number of patients and control subjects.

In the last years, much research has been done in the field of non-linear dynamics. Most of these studies have been carried out applying the D_2 (Stam et al., 1995; Besthorn et al., 1995, 1997; Jeong et al., 1998; Jelles et al., 1999; Jeong et al., 2001a) or the first positive Lyapunov exponent (Jeong et al., 1998, 2001a). Measures such as D_2 , K-S entropy, the Lyapunov spectrum and related algorithms have been much studied in the presence of noise and limited data. Most of these methods successfully use dimensions larger than $m=1$ or $m=2$, as is typically employed with $ApEn$. Thus, in the *purely deterministic dynamical system* for which these methods were developed, they reconstruct the probability structure of the space with greater detail than $ApEn$ does. However, in the general stochastic, noisy deterministic or composite setting, the statistical accuracy of the aforementioned measures is typically very poor (Pincus,

1991). Because dynamic mechanics of most biological signals remain undefined, a suitable statistic of regularity for these signals must be more cautious to accommodate general classes of processes and their much more diffuse reconstructed dynamics (Pincus, 2001). On the other hand, *ApEn* is finite for stochastic, noisy deterministic and composite processes and can be applied to short time series with good statistical reproducibility. The potential uses of *ApEn* to provide new insights in epidemiological settings are thus considerable from a complementary perspective to that given by more classical statistical methods. It appears that *ApEn* has potential widespread utility to practical data analysis and clinical application due to the salient features it bears (Pincus, 2001). Moreover, when applied to the analysis of biomedical time series, *ApEn* does not show the important drawbacks that many widely used non-linear methods (D_2 , first positive Lyapunov exponent) have.

Some limitations of our study merit consideration. First of all, the sample size was small. Thus, a false negative (missed finding) or type II error cannot be excluded due to the wider confidence interval associated with the small sample size. Furthermore, in our study we set a strict significance level ($\alpha=0.01$) to minimize the type I error and this would have also increased the probability of a type II error. As a result of this shortcomings, our findings are preliminary. Hence, to prove the usefulness of *ApEn* as a diagnostic tool, this approach should be extended on a much larger patient population before any conclusion can be made of its clinical diagnostic value. 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 sleep (Burioka et al., 2003), anaesthesia (Zhang and Roy, 2001) and epilepsy (Radhakrishnan and Gangadhar, 1998). Ageing and age-related diseases often accompany a wide-ranging loss of physiological complexity (Kyriazis, 2003). The disruptions of fractal and non-linear physiological properties lead to an increase in regularity and stochasticity, a situation encountered during ageing and age-related diseases (Goldberger et al., 2002). Thus, although this pilot study shows that *ApEn* might be a helpful tool for recognition of AD, further work must be carried out to examine non-linear EEG activity in other types of dementia.

It should also be mentioned that *ApEn* is sensitive to the quantification of noise by mistake. To avoid a significant contribution of noise in *ApEn* calculation, one must choose r larger than most of the noise (Pincus, 1991) and be careful with the selection of EEG epochs. Thus, off-line we selected artefact-free EEG epochs that 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 *ApEn* and relative power calculations. Furthermore, we used $r=0.2$ times the SD of the time series, as *ApEn* is nearly unaffected by noise of magnitude below that r level and is also robust to outliers. For r values larger than 0.25 times the SD of the data, too much detailed system information is lost (Pincus, 1991).

It is important to note that this preliminary study represents only a first step in demonstrating the feasibility of *ApEn* for recognition of AD. Non-linear dynamics suggest that AD can be a dynamical disease which is characterized by changes in the qualitative dynamics of physiological processes (Jeong, 2004). We wanted to test the hypothesis that the irregularity (or complexity) of the EEG of patients with a diagnosis of AD is lower than that of age-matched controls hence indicating an abnormal type of dynamics in this group. Although conclusions are somewhat limited by the small sample size, our experimental results prove the potential applications of *ApEn* and indicate that the degree of irregularity or complexity of AD patients' EEGs is significantly lower (lower *ApEn* values) than that of control subjects in the parietal region. A decrease in *ApEn* in the EEG of AD patients may be interpreted as

“decomplexification” or “loss of irregularity” associated with a general effect of neurotransmitter deficiency and loss of connectivity of local neural networks as a result of nerve cell death. Moreover, the comparison of *ApEn* results with spectral analysis indicates that this method might be a complementary tool to more conventional EEG measures. Nevertheless, further studies with a larger sample size are required to substantiate this suggestion.

Finally, although non-linear EEG analysis cannot yet be applied as a diagnostic tool, our findings are important from a theoretical point of view. They show the possibility to analyse the dynamical behaviour of the brain and to find differences between AD patients and control subjects with *ApEn*. *ApEn* might be a powerful tool to reveal hidden characteristics of biosignals that can remain undetected with linear (spectral) analysis, as physiological systems are basically non-linear in nature. We expect that non-linear analysis will give us a deeper understanding of the brain function in ways which are not possible by more classical and conventional statistical methods. Further work is now required to test the potential value of our methodology prospectively (i.e. apply our methodology to a new and larger data set). Future lines of research also include the comparison of *ApEn* in the EEG of AD patients with other entropy estimators.

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Figure legends

Figure 1. ROC curves to discriminate AD patients and control subjects at the electrodes in which $p < 0.01$ (P3 and P4). The ROC curve values are marked with an asterisk and the interpolating parametric cubic spline curve is superimposed. (A) P3. (B) P4.

Tables

Table 1

Sociodemographic data of the control subjects and patients with AD. Mini-Mental State Examination (MMSE) scores and the results of the visual analyses of the patients' EEGs are also shown. The patients that were receiving lorapezlam are marked with an asterisk

AD PATIENTS					CONTROL SUBJECTS			
Identification	Age	Sex	MMSE	Visual analysis of the EEG	Identification	Age	Sex	MMSE
Alz-1	80	F	7/30	Moderate slowing	Con-1	72	M	30/30
Alz-2*	69	F	7/30	Moderate slowing	Con-2	76	M	30/30
Alz-3	71	F	7/30	Normal	Con-3	70	M	30/30
Alz-4	74	M	20/30	Normal	Con-4	67	F	30/30
Alz-5	79	F	10/30	Moderate slowing	Con-5	76	F	30/30
Alz-6*	72	M	7/30	Mild slowing	Con-6	86	M	30/30
Alz-7	77	M	14/30	Mild slowing	Con-7	79	M	30/30
Alz-8	79	F	17/30	Moderate slowing	Con-8	73	M	30/30
Alz-9	76	M	23/30	Mild slowing				
Alz-10	71	F	14/30	Mild slowing				
Mean $\pm$ SD	74.8 $\pm$ 3.9		12.6 $\pm$ 5.9/30		Mean $\pm$ SD	74.9 $\pm$ 5.9		30.0 $\pm$ 0.0/30

Table 2

The average *ApEn* values (Mean $\pm$ SD) of the EEGs for the AD patients and control subjects for all channels. Significant group differences are marked with an asterisk.

Electrode	AD patients	Control subjects	Statistical analysis
			<i>p</i> value
F3	0.80 $\pm$ 0.14	0.88 $\pm$ 0.20	0.361
F4	0.85 $\pm$ 0.16	0.86 $\pm$ 0.25	0.927
F7	0.89 $\pm$ 0.17	0.86 $\pm$ 0.19	0.747
F8	0.89 $\pm$ 0.17	0.92 $\pm$ 0.21	0.714
Fp1	0.71 $\pm$ 0.26	0.88 $\pm$ 0.20	0.140
Fp2	0.72 $\pm$ 0.17	0.88 $\pm$ 0.22	0.103
T3	1.07 $\pm$ 0.24	1.09 $\pm$ 0.33	0.881
T4	1.11 $\pm$ 0.35	1.10 $\pm$ 0.26	0.931
T5	0.84 $\pm$ 0.23	1.07 $\pm$ 0.23	0.049
T6	0.85 $\pm$ 0.25	1.06 $\pm$ 0.21	0.079
C3	0.86 $\pm$ 0.17	1.03 $\pm$ 0.18	0.049
C4	0.89 $\pm$ 0.17	1.03 $\pm$ 0.14	0.087
P3*	0.74 $\pm$ 0.19	1.05 $\pm$ 0.16	0.002
P4*	0.78 $\pm$ 0.19	1.05 $\pm$ 0.15	0.005
O1	0.86 $\pm$ 0.22	1.10 $\pm$ 0.21	0.032
O2	0.85 $\pm$ 0.23	1.08 $\pm$ 0.21	0.040

Table 3

The intersubject and intrasubject coefficients of variation of *ApEn* results for the AD patients and control subjects for all channels.

Electrode	Intersubject coefficient of variation		Intrasubject coefficient of variation (Mean $\pm$ SD)	
	AD patients	Control subjects	AD patients	Control subjects
F3	17.73%	22.15%	21.74 $\pm$ 12.17%	18.29 $\pm$ 9.70%
F4	18.76%	28.63%	21.32 $\pm$ 9.70%	15.75 $\pm$ 6.62%
F7	19.31%	22.15%	23.70 $\pm$ 11.27%	18.30 $\pm$ 5.05%
F8	19.57%	22.64%	21.65 $\pm$ 9.47%	15.93 $\pm$ 4.18%
Fp1	36.07%	22.46%	34.51 $\pm$ 19.64%	20.94 $\pm$ 5.20%
Fp2	23.27%	25.26%	28.45 $\pm$ 10.58%	19.66 $\pm$ 7.68%
T3	22.38%	30.01%	17.97 $\pm$ 8.11%	11.68 $\pm$ 4.53%
T4	31.77%	24.10%	15.03 $\pm$ 12.28%	10.09 $\pm$ 7.01%
T5	27.37%	21.24%	16.54 $\pm$ 7.73%	11.20 $\pm$ 7.50%
T6	30.00%	20.31%	17.40 $\pm$ 10.70%	9.67 $\pm$ 4.95%
C3	19.80%	17.38%	23.23 $\pm$ 13.06%	11.36 $\pm$ 4.66%
C4	18.67%	13.41%	21.81 $\pm$ 14.74%	12.77 $\pm$ 5.28%
P3	26.44%	15.40%	19.48 $\pm$ 10.93%	9.85 $\pm$ 4.99%
P4	24.33%	14.30%	16.22 $\pm$ 8.54%	8.49 $\pm$ 3.58%
O1	25.65%	18.88%	14.00 $\pm$ 7.80%	9.43 $\pm$ 7.54%
O2	26.63%	19.25%	14.63 $\pm$ 7.13%	11.11 $\pm$ 6.76%

Table 4

Relative power values (Mean $\pm$ SD) in the delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (13–30 Hz) frequency bands for AD patients and control subjects. Significant group differences are marked with an asterisk.

DELTA BAND (0.5-4 Hz)				THETA BAND (4-8 Hz)			
Electrode	AD patients	Control subjects	Statistical analysis	Electrode	AD patients	Control subjects	Statistical analysis
			<i>p</i> value				<i>p</i> value
F3	0.74 $\pm$ 0.16	0.74 $\pm$ 0.13	0.980	F3	0.12 $\pm$ 0.06	0.07 $\pm$ 0.01	0.049
F4	0.74 $\pm$ 0.17	0.62 $\pm$ 0.17	0.131	F4	0.11 $\pm$ 0.06	0.08 $\pm$ 0.02	0.233
F7	0.72 $\pm$ 0.14	0.68 $\pm$ 0.16	0.548	F7	0.11 $\pm$ 0.05	0.08 $\pm$ 0.02	0.190
F8	0.72 $\pm$ 0.14	0.64 $\pm$ 0.18	0.309	F8	0.12 $\pm$ 0.06	0.09 $\pm$ 0.03	0.258
Fp1	0.76 $\pm$ 0.15	0.72 $\pm$ 0.20	0.670	Fp1	0.10 $\pm$ 0.05	0.07 $\pm$ 0.02	0.112
Fp2	0.79 $\pm$ 0.14	0.66 $\pm$ 0.17	0.091	Fp2	0.10 $\pm$ 0.05	0.08 $\pm$ 0.02	0.416
T3	0.66 $\pm$ 0.20	0.52 $\pm$ 0.18	0.145	T3	0.12 $\pm$ 0.06	0.09 $\pm$ 0.05	0.435
T4*	0.68 $\pm$ 0.14	0.46 $\pm$ 0.14	0.004	T4	0.12 $\pm$ 0.06	0.10 $\pm$ 0.04	0.470
T5	0.71 $\pm$ 0.14	0.56 $\pm$ 0.18	0.069	T5	0.15 $\pm$ 0.07	0.10 $\pm$ 0.05	0.113
T6	0.71 $\pm$ 0.18	0.49 $\pm$ 0.24	0.043	T6	0.12 $\pm$ 0.06	0.10 $\pm$ 0.05	0.404
C3	0.75 $\pm$ 0.16	0.63 $\pm$ 0.23	0.223	C3	0.11 $\pm$ 0.07	0.08 $\pm$ 0.04	0.290
C4	0.74 $\pm$ 0.17	0.63 $\pm$ 0.25	0.291	C4	0.11 $\pm$ 0.06	0.08 $\pm$ 0.03	0.232
P3	0.72 $\pm$ 0.18	0.53 $\pm$ 0.22	0.071	P3	0.14 $\pm$ 0.09	0.11 $\pm$ 0.10	0.524
P4*	0.70 $\pm$ 0.20	0.39 $\pm$ 0.21	0.006	P4	0.13 $\pm$ 0.06	0.10 $\pm$ 0.05	0.298
O1	0.67 $\pm$ 0.15	0.46 $\pm$ 0.23	0.032	O1	0.14 $\pm$ 0.06	0.08 $\pm$ 0.03	0.023
O2*	0.69 $\pm$ 0.14	0.40 $\pm$ 0.20	0.003	O2	0.13 $\pm$ 0.06	0.10 $\pm$ 0.05	0.219
ALPHA BAND (8-13 Hz)				BETA BAND (13-30 Hz)			
Electrode	AD patients	Control subjects	Statistical analysis	Electrode	AD patients	Control subjects	Statistical analysis
			<i>p</i> value				<i>p</i> value
F3	0.07 $\pm$ 0.06	0.09 $\pm$ 0.07	0.499	F3	0.07 $\pm$ 0.05	0.09 $\pm$ 0.08	0.428
F4	0.07 $\pm$ 0.05	0.13 $\pm$ 0.10	0.119	F4	0.07 $\pm$ 0.06	0.15 $\pm$ 0.09	0.036
F7	0.06 $\pm$ 0.05	0.12 $\pm$ 0.07	0.080	F7	0.08 $\pm$ 0.05	0.11 $\pm$ 0.09	0.394
F8	0.06 $\pm$ 0.04	0.11 $\pm$ 0.07	0.063	F8	0.08 $\pm$ 0.05	0.13 $\pm$ 0.08	0.098
Fp1	0.05 $\pm$ 0.04	0.09 $\pm$ 0.09	0.274	Fp1	0.07 $\pm$ 0.06	0.11 $\pm$ 0.11	0.419
Fp2	0.05 $\pm$ 0.04	0.10 $\pm$ 0.06	0.038	Fp2	0.06 $\pm$ 0.04	0.13 $\pm$ 0.09	0.032
T3*	0.06 $\pm$ 0.04	0.17 $\pm$ 0.09	0.003	T3	0.12 $\pm$ 0.11	0.18 $\pm$ 0.11	0.280
T4*	0.06 $\pm$ 0.04	0.17 $\pm$ 0.06	0.001	T4	0.10 $\pm$ 0.05	0.21 $\pm$ 0.12	0.013
T5	0.07 $\pm$ 0.04	0.20 $\pm$ 0.15	0.025	T5	0.06 $\pm$ 0.04	0.13 $\pm$ 0.07	0.027
T6	0.09 $\pm$ 0.08	0.22 $\pm$ 0.14	0.026	T6	0.07 $\pm$ 0.06	0.16 $\pm$ 0.14	0.064
C3	0.06 $\pm$ 0.05	0.12 $\pm$ 0.08	0.070	C3	0.07 $\pm$ 0.05	0.15 $\pm$ 0.16	0.144
C4	0.07 $\pm$ 0.05	0.12 $\pm$ 0.08	0.086	C4	0.08 $\pm$ 0.06	0.15 $\pm$ 0.17	0.222
P3	0.08 $\pm$ 0.07	0.20 $\pm$ 0.12	0.023	P3	0.06 $\pm$ 0.04	0.15 $\pm$ 0.15	0.095
P4	0.10 $\pm$ 0.10	0.32 $\pm$ 0.22	0.012	P4	0.07 $\pm$ 0.06	0.17 $\pm$ 0.15	0.053
O1	0.10 $\pm$ 0.07	0.28 $\pm$ 0.22	0.029	O1	0.07 $\pm$ 0.04	0.15 $\pm$ 0.10	0.048
O2	0.10 $\pm$ 0.08	0.29 $\pm$ 0.20	0.014	O2	0.07 $\pm$ 0.04	0.17 $\pm$ 0.11	0.014