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APPROXIMATE ENTROPY OF EEG BACKGROUND ACTIVITY IN ALZHEIMER'S DISEASE PATIENTS

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ABSTRACT—Non-linear analysis of the electroencephalogram (EEG) background activity can help to obtain a better understanding of abnormal dynamics in the brain. The aim of this study was to analyze the regularity of the EEG time series 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. We recorded the EEG from 19 scalp electrodes in 11 AD patients and 11 age-matched controls and estimated the Approximate Entropy (*ApEn*). *ApEn* is a non-linear method that can be used to quantify the irregularity of a time series. Larger values correspond to more irregularity. We evaluated different values for input parameters m and r to estimate *ApEn* and concluded that m=1 and r=0.25 times the SD of the time series were the optimum choices. With these parameters, *ApEn* was significantly lower in the AD patients at the P3, P4, O1 and O2 (p<0.01) electrodes. The decreased irregularity found in the EEG of AD patients in the parietal and occipital regions leads us to think that regularity analysis of the EEG with *ApEn* could be a useful tool to increase our insight into brain dysfunction in Alzheimer's disease.

Key Words: Alzheimer's disease; EEG; Non-linear analysis; Approximate Entropy; Regularity

1. INTRODUCTION

Alzheimer's disease (AD) is a primary degenerative dementia of unknown etiology that gradually destroys brain cells and represents the most prevalent form of dementia in western countries [1]. Clinically, AD manifests as a slowly progressive impairment of mental functions whose course lasts several years prior to the death of the patient [2]. Structural changes in AD are related to the accumulation of amyloid plaques between nerve cells in the brain and with the appearance of neurofibrillary tangles inside nerve cells, particularly in the hippocampus and the cerebral cortex [3]. 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 investigating dementias for several decades. AD patients' EEGs show a shift of the power spectrum to lower frequencies and

a decrease of coherence among cortical areas [2]. However, in the early stages of the disease the EEG may exhibit normal frequencies and be similar to that of elderly control subjects [4].

Recent progress in the theory of non-linear dynamics has provided new methods for the study of the EEG [2]. Non-linearity 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 behavior 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 EEG appears to be an appropriate area for non-linear time series analysis [5]. 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 [6]–[8]. Many investigations with non-linear methods have revealed possible medical applications for non-linear analysis.

In particular, several authors have analyzed the EEG in AD patients with non-linear methods. It has been shown that AD patients have lower correlation dimension (D_2) values – a measure of the underlying system dimensional complexity – than control subjects [9]–[11]. Furthermore, AD patients also have significantly lower values of the largest Lyapunov ($L1$) exponent than controls in almost all EEG channels [9]. However, estimating the non-linear dynamical complexity of physiological data using measures such as D_2 and $L1$ is problematic, as the amount of data required for meaningful results in their computation is beyond the experimental possibilities for physiological data [12]. Furthermore, the algorithms to estimate the aforementioned non-linear metrics assume the time series to be stationary and this is generally not true with biological data. Thus, the study of the EEG background activity with more suitable non-linear methods becomes necessary. For instance, mutual information analysis [13] and synchronization likelihood [14], [15] have been used to assess information transmission between different cortical areas in AD.

One 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. Kolmogorov-Sinai entropy (K-S entropy), developed by Kolmogorov and expanded upon by Sinai, allows classifying deterministic dynamical systems by rate of information generation [16]. Unfortunately, K-S entropy was not developed for statistical applications and its blind application to practical time series will only evaluate system noise, not underlying system properties, as it generally requires a vast amount of input data to achieve convergence [17].

Approximate Entropy (*ApEn*) is a recently introduced family of statistics that quantifies regularity in the data without any *a priori* knowledge about the system generating them [18]. It was defined by Pincus [19], motivated by applications to short and noisy data sets (it is applicable to systems with at least 50 data points), along with thematically similar lines to K-S entropy. However, the focus was different: to provide a widely applicable, statistically valid formula that will distinguish data sets by a measure of regularity [19].

The present study was undertaken to examine the EEG background activity in AD with *ApEn*. We wanted to test the hypothesis that the irregularity of the AD patients' EEG is lower than that of age-matched controls, hence indicating an abnormal type of dynamics in this group.

2. MATERIAL AND METHODS

2.1 Subjects

Twenty-two subjects participated in this study. Informed consent was obtained from all control subjects and all caregivers of the demented patients. The study was approved by the local ethics committee.

Eleven patients (5 men and 6 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 EEGs were recorded. The diagnosis was made on the basis of exhaustive medical, physical, neurological, psychiatric and neuropsychological examinations. Mini-Mental State Examination (MMSE) was used to assess the cognitive function [20]. The mean MMSE score for the patients was 13.1 ± 5.9 (Mean ± SD). Five of them had a score of less than 12 points, indicating a severe degree of dementia. Two patients were receiving lorapezam. Although with therapeutic doses, benzodiapzepines may enhance beta activity, 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 (7 men and 4 women; age = 72.8 ± 6.1 years, mean ± SD). The MMSE score value was 30 in all control subjects.

2.2 EEG Recording

EEGs were recorded from the 19 scalp loci of the international 10-20 system (electrodes F3, F4, F7, F8, Fp1, Fp2, T3, T4, T5, T6, C3, C4, P3, P4, O1, O2, Fz, Cz and Pz) using a Profile Study Room 2.3.411 EEG equipment (Oxford Instruments). More than five minutes of data were recorded from each subject. The 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 artifact-free EEG data as possible.

All EEGs were visually inspected by a specialist physician to check for eye movement and other artifacts. Only EEG data free from electrooculographic and movement artifacts and with minimal electromyographic (EMG) activity were selected for non-linear analysis. EEGs were then organized in 5 second epochs (1280 points). An average number of 30.0 ± 12.5 artifact-free epochs (Mean ± SD) were selected from each electrode for each subject and copied as ASCII files for off-line analysis on a personal computer. Furthermore, prior to the *ApEn* estimation, 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 residual EMG activity.

2.3 Approximate Entropy

ApEn was introduced as a quantification of regularity in sequences and time series, initially motivated by applications to relatively short, noisy data sets [19]. It provides a finite sequence formulation of randomness, via proximity to maximal irregularity [21], [22]. Moreover, *ApEn* is scale invariant and model independent, evaluates both dominant and subordinated patterns in data, and discriminates series for which clear feature recognition is difficult [23]. Notably, it detects changes in underlying episodic behavior not reflected in peak occurrences or amplitudes [24]. *ApEn* can be applied to discriminate both general classes of correlated stochastic processes, as well as noisy deterministic systems, and it is nearly unaffected by low level noise [23]. Furthermore, it is complementary to spectral and autocorrelation analyses, providing effective discriminatory capability in instances in which the aforementioned measures exhibit minimal distinctions [23], [25].

ApEn assigns a non-negative number to a time series, with larger values corresponding to more irregularity in the data. Two input parameters, a run length m and a tolerance window r, must be specified to compute *ApEn*. Briefly, *ApEn* measures the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same r) on subsequent incremental comparisons. It is important to consider $ApEn(m, r, N)$, where N is the number of points of the time series, as a family of characterizing measures: comparisons between

time series can only be made with the same values of m, r and N [23]. Given N data points from a time series $\{x(n)\} = x(1), x(2), \ldots, x(N)$, one should follow these steps to compute *ApEn* [23]:

1. Form N-m+1 vectors $X(1)\ldots X(N\text{-}m\text{+}1)$ defined by: $X(i) = [x(i), x(i+1),\ldots, x(i+m\text{-}1)]$, $i = 1\ldots N\text{-}m\text{+}1$.
2. Define the distance between $X(i)$ and $X(j)$, $d[X(i),X(j)]$, as the maximum norm:

$$d[X(i),X(j)] = \max_{k=1,2,\ldots m} |x(i+k-1)-x(j+k-1)| \quad (1)$$

3. For a given $X(i)$, count the number of j ($j = 1\ldots N\text{-}m\text{+}1$) so that $d[X(i), X(j)] \le r$, denoted as $N^m(i)$. Then, for $i=1\ldots N\text{-}m\text{+}1$,

$$C_r^m(i) = N^m(i)/(N-m+1) \quad (2)$$

$C_r^m(i)$ measures, within a tolerance r, the frequency of patterns similar to a given one of window length m.

4. Compute the natural logarithm of each $C_r^m(i)$, and average it over i,

$$\phi^m(r) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1} \ln C_r^m(i) \quad (3)$$

5. Increase the dimension to m+1. Repeat steps 1) to 4) and find $C_r^{m+1}(i)$ and $\phi^{m+1}(r)$.
6. We define *ApEn* by:

$$ApEn(m,r,N) = \phi^m(r) - \phi^{m+1}(r) \quad (4)$$

Although m and r are critical in determining the outcome of *ApEn*, 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. This condition can be fulfilled by choosing small m (short templates) and large r (wide tolerance). However, there are penalties for criteria that are too relaxed [19]. For smaller r values, one usually achieves poor conditional probability estimates, while for larger r values, too much detailed system information is lost. To avoid a significant contribution of noise in an *ApEn* calculation, one must choose r larger than most of the noise [19]. It has been 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 standard deviation (SD) of the original data sequence $\{x(n)\}$ [23]. 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 [23]. Moreover, it has been demonstrated that these input parameters produce good statistical reproducibility for *ApEn* for time series of length $N \ge 60$, as considered herein [19], [24]. *ApEn* was calculated with a short computer program written in MATLAB®.

2.4 Statistical Analysis

Student's *t*-test was used to evaluate the statistical differences between the *ApEn* values for AD patients and control subjects. Differences were considered statistically significant if the p value was lower than 0.01.

The ability to discriminate AD patients from control subjects at the electrodes where $p < 0.01$ was evaluated using Receiver Operating Characteristic (ROC) curves [26]. We define sensitivity as the rate of patients with a diagnosis of AD who test positive (i.e. the true positive rate), whereas specificity represents the fraction of controls correctly recognized (i.e. the true negative rate). We used a computer program developed with MATLAB® that automatically selected different cut-off points (*ApEn* values) 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. Using these curves, we selected an optimum threshold as the cut-off point in which the highest accuracy (minimal false negative and false positive results) was obtained. It was determined graphically from the ROC curve as the closest value to the left top point (100% sensitivity, 100% specificity).

3. RESULTS

ApEn was estimated at channels Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5 and T6 with $m = 1$, $m = 2$ and r a fixed value between 0.1 and 0.25 times the SD of the original data sequence. Results were averaged based on all the artifact-free 5 second epochs within the five-minute period of EEG recordings. The average *ApEn* values for both groups and the *p*-values of the Student's *t*-test performed to examine the differences between them for the 16 analyzed electrodes are summarized in Table I (m=1) and Table II (m=2).

With m=1 and all different combinations of r values (0.1, 0.15, 0.2 and 0.25 times the SD of the analyzed epoch) significant differences between both groups were found at electrodes P3, P4, O1 and O2. However, that was not the case with m=2. With that run length and r=0.2 times the SD, significant differences between both groups were only found at electrode P3. Results improved with m=2 and r=0.25 times the SD, as significant differences were found at electrodes P3, P4 and O1. These results suggest that the choice of m and r is critical to find the subtle differences that might exist between the EEG background activity in AD patients and control subjects.

Finally, we evaluated the ability of *ApEn* to discriminate AD patients from control subjects at the electrodes in which significant differences were found using ROC plots. Our objective was to determine the optimum threshold (*ApEn* value) that maximized the diagnostic accuracy. As an example, Figure 1 represents the ROC curves corresponding to *ApEn*(m=1, r=0.25 times the SD) at electrodes P3, P4, O1 and O2. When *ApEn* was estimated with m=1 the accuracy was 77.27% at electrodes P3, O1 and O2 and 72.73% at P4. Sensitivities varied between 90.91% at electrode O2 for all possible combinations of r and m fixed to 1 and 63.64% at P4 when m=1 and r=0.25 times the SD of the time series. However, it must be noted that an excellent sensitivity at O2 had a low specificity associated. Specificities ranged between 63.64% at electrode O2 and 81.82% at P3. When *ApEn* was estimated with m=2 and r=0.25 times the SD of the data, we obtained an accuracy of 81.82% at electrode P3, with a specificity of 100%, meaning that all control subjects could be correctly classified by the method. Table III summarizes these results. Furthermore, it also includes the *ApEn* value that maximizes the accuracy obtained with the ROC curves and the area under the ROC curve (AROC). The AROC curve can be used to classify the precision of a diagnostic test. An AROC of 0.8595 means that a randomly selected individual from the control subjects' group has an *ApEn* value larger than that of a randomly chosen individual from the AD patients' group in 85.95% of the time [26]. Usually, larger AROCs are associated with better diagnostic tests. Hence, according to the AROC, the best results are those obtained with m=1 at electrodes P3 and O1 (AROC=0.8595).

4. DISCUSSION AND CONCLUSIONS

The diagnosis of AD, the main cause of dementia in western countries, is becoming an increasingly important problem for clinical medicine as new therapies emerge. In this pilot study we analyzed the EEG background activity of 11 control subjects and 11 AD patients with *ApEn*, a family of statistics that evaluates the regularity in time series, with larger values corresponding to more irregularity in the data. We have found that AD patients have lower *ApEn* values than

Table I. Average *ApEn* values with *m*=1. Significant differences ($p < 0.01$) are marked with an asterisk.

***r*=0.1 times the SD**				***r*=0.15 times the SD**			
E	AD patients (Mean ± SD)	Control subjects (Mean ± SD)	*p*-value	E	AD patients (Mean ± SD)	Control subjects (Mean ± SD)	*p*-value
F3	1.3663 ± 0.1642	1.4995 ± 0.2142	0.1172	F3	1.0250 ± 0.1547	1.1558 ± 0.2131	0.1150
F4	1.4452 ± 0.1816	1.4666 ± 0.2481	0.8198	F4	1.1031 ± 0.2010	1.1215 ± 0.2451	0.8489
F7	1.4884 ± 0.1928	1.5381 ± 0.2503	0.6078	F7	1.1477 ± 0.1900	1.1941 ± 0.2468	0.6271
F8	1.4892 ± 0.1887	1.5623 ± 0.2143	0.4055	F8	1.1453 ± 0.1860	1.2154 ± 0.2118	0.4193
Fp1	1.2374 ± 0.3395	1.4781 ± 0.1902	0.0536	Fp1	0.9202 ± 0.2908	1.1328 ± 0.1902	0.0559
Fp2	1.2820 ± 0.1970	1.4490 ± 0.2623	0.1068	Fp2	0.9486 ± 0.1828	1.1063 ± 0.2590	0.1144
T3	1.7017 ± 0.2676	1.7323 ± 0.3411	0.8169	T3	1.3601 ± 0.2718	1.3935 ± 0.3354	0.8006
T4	1.7041 ± 0.3399	1.7108 ± 0.2821	0.9604	T4	1.3653 ± 0.3464	1.3683 ± 0.2839	0.9823
T5	1.4430 ± 0.2617	1.6979 ± 0.2120	0.0207	T5	1.1004 ± 0.2549	1.3546 ± 0.2140	0.0198
T6	1.4345 ± 0.2733	1.6829 ± 0.2292	0.0316	T6	1.0934 ± 0.2660	1.3379 ± 0.2300	0.0319
C3	1.4771 ± 0.2476	1.6197 ± 0.1790	0.1373	C3	1.1375 ± 0.2394	1.2731 ± 0.1841	0.1521
C4	1.5271 ± 0.2503	1.6347 ± 0.1446	0.2313	C4	1.1867 ± 0.2469	1.2882 ± 0.1491	0.2568
P3*	1.3303 ± 0.2502	1.6488 ± 0.1380	0.0014	P3*	0.9938 ± 0.2364	1.3020 ± 0.1423	0.0014
P4*	1.3802 ± 0.2364	1.6540 ± 0.1403	0.0036	P4*	1.0390 ± 0.2255	1.3068 ± 0.1439	0.0034
O1*	1.4543 ± 0.2283	1.7661 ± 0.1841	0.0021	O1*	1.1100 ± 0.2268	1.4219 ± 0.1906	0.0023
O2*	1.4382 ± 0.2345	1.7247 ± 0.2189	0.0077	O2*	1.0939 ± 0.2318	1.3804 ± 0.2233	0.0079
***r*=0.2 times the SD**				***r*=0.25 times the SD**			
E	AD patients (Mean ± SD)	Control subjects (Mean ± SD)	*p*-value	E	AD patients (Mean ± SD)	Control subjects (Mean ± SD)	*p*-value
F3	0.7921 ± 0.1374	0.9136 ± 0.2002	0.1128	F3	0.6288 ± 0.1181	0.7378 ± 0.1821	0.1115
F4	0.8643 ± 0.1572	0.8819 ± 0.2268	0.8349	F4	0.6933 ± 0.1371	0.7100 ± 0.2028	0.8242
F7	0.9086 ± 0.1789	0.9507 ± 0.2299	0.6374	F7	0.7349 ± 0.1634	0.7732 ± 0.2072	0.6355
F8	0.9047 ± 0.1733	0.9682 ± 0.1975	0.4323	F8	0.7309 ± 0.1563	0.7867 ± 0.1775	0.4426
Fp1	0.7101 ± 0.2423	0.8915 ± 0.1803	0.0602	Fp1	0.5641 ± 0.2006	0.7182 ± 0.1649	0.0631
Fp2	0.7274 ± 0.1602	0.8688 ± 0.2423	0.1220	Fp2	0.5745 ± 0.1363	0.6994 ± 0.2194	0.1243
T3	1.1110 ± 0.2627	1.1462 ± 0.3142	0.7788	T3	0.9236 ± 0.2472	0.9580 ± 0.2869	0.7663
T4	1.1189 ± 0.3359	1.1181 ± 0.2702	0.9950	T4	0.9342 ± 0.3186	0.9296 ± 0.2485	0.9701
T5	0.8633 ± 0.2346	1.1028 ± 0.2073	0.0196	T5	0.6936 ± 0.2081	0.9125 ± 0.1953	0.0193
T6	0.8586 ± 0.2444	1.0869 ± 0.2190	0.0318	T6	0.6914 ± 0.2179	0.8976 ± 0.2018	0.0322
C3	0.9002 ± 0.2186	1.0227 ± 0.1786	0.1658	C3	0.7291 ± 0.1954	0.8363 ± 0.1670	0.1820
C4	0.9457 ± 0.2329	1.0371 ± 0.1462	0.2833	C4	0.7703 ± 0.2150	0.8490 ± 0.1384	0.3198
P3*	0.7672 ± 0.2104	1.0497 ± 0.1397	0.0014	P3*	0.6088 ± 0.1817	0.8599 ± 0.1331	0.0014
P4*	0.8063 ± 0.2023	1.0547 ± 0.1402	0.0032	P4*	0.6423 ± 0.1753	0.8644 ± 0.1320	0.0031
O1*	0.8706 ± 0.2131	1.1666 ± 0.1876	0.0025	O1*	0.6989 ± 0.1939	0.9714 ± 0.1801	0.0027
O2*	0.8560 ± 0.2163	1.1277 ± 0.2173	0.0081	O2*	0.6867 ± 0.1961	0.9357 ± 0.2051	0.0086

E: Electrode; SD: Standard deviation

Table II. Average *ApEn* values with *m*=2. Significant differences ($p < 0.01$) are marked with an asterisk.

***r*=0.1 times the SD**				***r*=0.15 times the SD**			
E	AD patients (Mean ± SD)	Control subjects (Mean ± SD)	*p*-value	E	AD patients (Mean ± SD)	Control subjects (Mean ± SD)	*p*-value
F3	0.8281 ± 0.0474	0.8863 ± 0.1032	0.1045	F3	0.7094 ± 0.0426	0.7628 ± 0.0890	0.0879
F4	0.8577 ± 0.0937	0.8797 ± 0.0925	0.5862	F4	0.7395 ± 0.0748	0.7534 ± 0.0796	0.6774
F7	0.9164 ± 0.1169	0.9169 ± 0.1197	0.9930	F7	0.7887 ± 0.1046	0.7938 ± 0.1078	0.9104
F8	0.9110 ± 0.1242	0.9360 ± 0.1158	0.6305	F8	0.7882 ± 0.1068	0.8060 ± 0.1044	0.6972
Fp1	0.7963 ± 0.1464	0.8969 ± 0.1057	0.0796	Fp1	0.6702 ± 0.1412	0.7717 ± 0.0902	0.0581
Fp2	0.8227 ± 0.0722	0.8872 ± 0.1310	0.1681	Fp2	0.6959 ± 0.0663	0.7645 ± 0.1206	0.1143
T3	1.0065 ± 0.1355	1.0003 ± 0.1590	0.9230	T3	0.8872 ± 0.1341	0.8840 ± 0.1610	0.9606
T4	0.9989 ± 0.1337	0.9999 ± 0.1375	0.9872	T4	0.8820 ± 0.1502	0.8743 ± 0.1282	0.8990
T5	0.8632 ± 0.1263	0.9341 ± 0.1357	0.2191	T5	0.7463 ± 0.1046	0.8206 ± 0.1238	0.1439
T6	0.8560 ± 0.1308	0.9491 ± 0.1395	0.1217	T6	0.7445 ± 0.1152	0.8300 ± 0.1169	0.0992
C3	0.8633 ± 0.1222	0.9143 ± 0.0685	0.2411	C3	0.7491 ± 0.1099	0.7900 ± 0.0599	0.2909
C4	0.8836 ± 0.1238	0.9126 ± 0.0735	0.5124	C4	0.7679 ± 0.1225	0.7888 ± 0.0572	0.6127
P3	0.7824 ± 0.1032	0.8921 ± 0.1013	0.0205	P3	0.6827 ± 0.0827	0.7783 ± 0.0748	0.0101
P4	0.7913 ± 0.0878	0.8840 ± 0.1207	0.0528	P4	0.6949 ± 0.0714	0.7771 ± 0.0897	0.0273
O1	0.8559 ± 0.1040	0.9683 ± 0.1426	0.0476	O1	0.7431 ± 0.0921	0.8558 ± 0.1308	0.0299
O2	0.8484 ± 0.1084	0.9682 ± 0.1476	0.0423	O2	0.7374 ± 0.0954	0.8530 ± 0.1328	0.0294
***r*=0.2 times the SD**				***r*=0.25 times the SD**			
E	AD patients (Mean ± SD)	Control subjects (Mean ± SD)	*p*-value	E	AD patients (Mean ± SD)	Control subjects (Mean ± SD)	*p*-value
F3	0.6289 ± 0.0484	0.6756 ± 0.0736	0.0935	F3	0.5645 ± 0.0573	0.6105 ± 0.0700	0.1070
F4	0.6570 ± 0.0632	0.6654 ± 0.0742	0.7765	F4	0.5931 ± 0.0641	0.5973 ± 0.0788	0.8909
F7	0.6923 ± 0.0856	0.7001 ± 0.0920	0.8398	F7	0.6190 ± 0.0765	0.6285 ± 0.0875	0.7902
F8	0.6937 ± 0.0833	0.7101 ± 0.0861	0.6548	F8	0.6198 ± 0.0728	0.6389 ± 0.0792	0.5640
Fp1	0.5810 ± 0.1396	0.6798 ± 0.0713	0.0497	Fp1	0.5124 ± 0.1385	0.6091 ± 0.0641	0.0486
Fp2	0.6068 ± 0.0687	0.6721 ± 0.1021	0.0937	Fp2	0.5361 ± 0.0740	0.5994 ± 0.0953	0.0974
T3	0.7770 ± 0.1120	0.7746 ± 0.1397	0.9648	T3	0.6936 ± 0.0958	0.6930 ± 0.1280	0.9890
T4	0.7732 ± 0.1289	0.7662 ± 0.1065	0.8909	T4	0.6891 ± 0.1123	0.6860 ± 0.0964	0.9466
T5	0.6617 ± 0.0896	0.7325 ± 0.0937	0.0852	T5	0.5948 ± 0.0900	0.6690 ± 0.0743	0.0478
T6	0.6587 ± 0.0997	0.7361 ± 0.0910	0.0718	T6	0.5904 ± 0.0975	0.6682 ± 0.0787	0.0526
C3	0.6650 ± 0.0952	0.7035 ± 0.0480	0.2453	C3	0.5998 ± 0.0903	0.6411 ± 0.0452	0.1898
C4	0.6819 ± 0.1036	0.7040 ± 0.0402	0.5178	C4	0.6161 ± 0.0920	0.6439 ± 0.0333	0.3580
P3*	0.6110 ± 0.0784	0.7015 ± 0.0491	0.0041	P3*	0.5498 ± 0.0850	0.6461 ± 0.0360	0.0025
P4	0.6247 ± 0.0699	0.7021 ± 0.0610	0.0119	P4*	0.5657 ± 0.0785	0.6475 ± 0.0455	0.0072
O1	0.6623 ± 0.0769	0.7619 ± 0.0982	0.0155	O1*	0.5977 ± 0.0743	0.6939 ± 0.0744	0.0066
O2	0.6568 ± 0.0803	0.7561 ± 0.1011	0.0190	O2	0.5921 ± 0.0785	0.6853 ± 0.0815	0.0129

E: Electrode; SD: Standard deviation

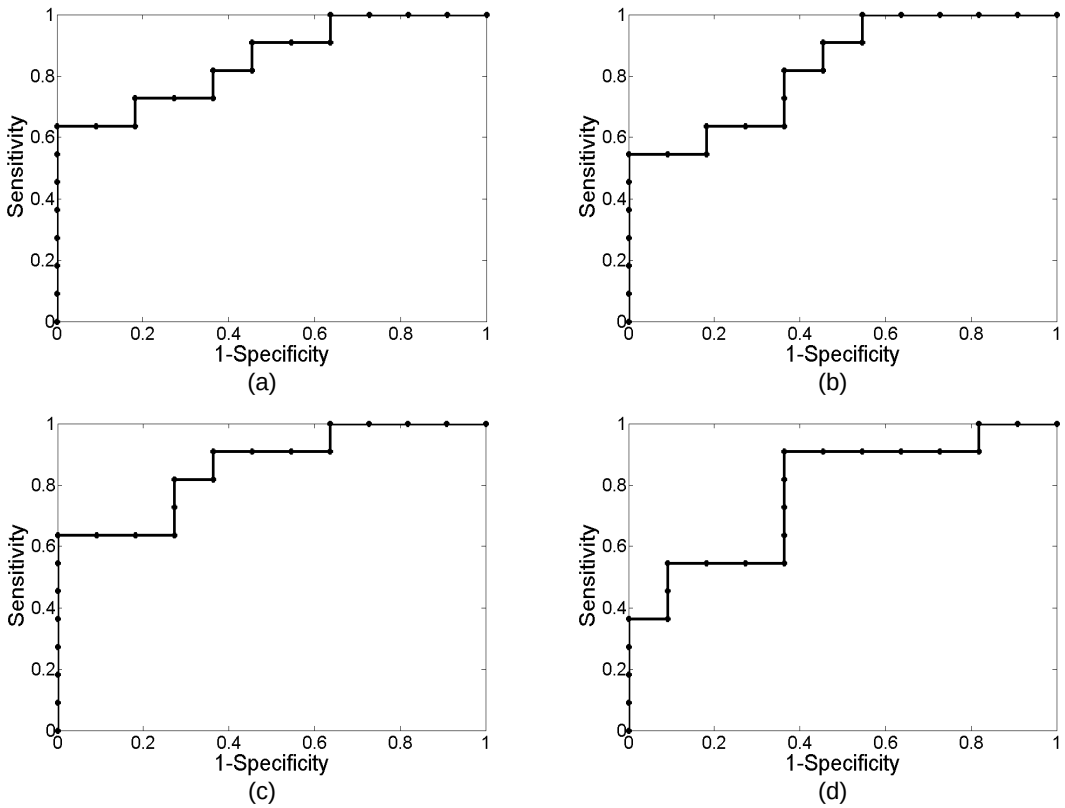

Figure 1. ROC curves for *ApEn*(*m*=1, *r*=0.25 times the SD) at the electrodes where $p < 0.01$. (a) P3. (b) P4. (c) O1. (d) O2.

control subjects at nearly all electrodes for all the studied combinations of m and r, with the exception of T3 and T4, where the mean *ApEn* values are sometimes slightly higher in AD patients. Furthermore, this study proves that the choice of m and r is critical to find significant differences. Our results show that estimating *ApEn* with m=1 allows us to detect more regularity differences between the EEG of AD patients and control subjects, irrespective of the r value, than m=2, where only relatively large r values are useful. Thus, it seems that choosing m=1 is necessary to discriminate series for which clear feature recognition is difficult and to detect subtle differences in the EEG background activity. To avoid a significant contribution of noise in an *ApEn* calculation, one must choose r larger than most of the noise [19]. Thus, despite that for m=1 all considered r values provided similar results, r=0.25 times the SD of the time series is the best option among them. Considering the results from this study, we infer that brains affected by AD show a more regular electrophysiological behavior, especially in the parietal and occipital regions.

Our results agree with other studies that have shown differences between the EEG background activity of AD patients and control subjects with non-linear analysis techniques. AD patients' EEGs have lower D_2 values than EEGs of control subjects [9–11], [27]. Consequently, AD patients are characterized by a less complex brain activity. Furthermore, it has been shown that AD patients have significantly lower $L1$ values than age-matched controls [9], [10]. Given the fact that the $L1$ of the EEG can be interpreted as a measure of flexibility of information processing

Table III. *ApEn* test results on the channels where significant differences ($p < 0.01$) between both groups were found. The optimum thresholds to discriminate AD patients and control subjects and the area under the ROC curves are included.

m and *r* values	Electrode	Threshold	Sensitivity (%)	Specificity (%)	Accuracy (%)	AROC
m=1, *r*=0.1	P3	1.5163	72.73	81.82	77.27	0.8595
	P4	1.5323	72.73	72.73	72.73	0.8347
	O1	1.5885	81.82	72.73	77.27	0.8595
	O2	1.6113	90.91	63.64	77.27	0.7769
m=1, *r*=0.15	P3	1.1661	72.73	81.82	77.27	0.8595
	P4	1.1849	72.73	72.73	72.73	0.8347
	O1	1.2460	81.82	72.73	77.27	0.8595
	O2	1.2621	90.91	63.64	77.27	0.7769
m=1, *r*=0.2	P3	0.9157	72.73	81.82	77.27	0.8595
	P4	0.9413	72.73	72.73	72.73	0.8347
	O1	0.9999	81.82	72.73	77.27	0.8595
	O2	1.0080	90.91	63.64	77.27	0.7769
m=1, *r*=0.25	P3	0.7326	72.73	81.82	77.27	0.8595
	P4	0.7381	63.64	81.82	72.73	0.8264
	O1	0.8181	81.82	72.73	77.27	0.8595
	O2	0.8190	90.91	63.64	77.27	0.7769
m=2, *r*=0.2	P3	0.6519	63.64	90.91	77.27	0.8017
m=2, *r*=0.25	P3	0.6081	63.64	100	81.82	0.8264
	P4	0.6166	81.82	72.73	77.27	0.8347
	O1	0.6219	63.64	90.91	77.27	0.8347

in the brain [28], decreased $L1$ values in AD patients reflect a drop in the flexibility of information processing in the injured brain [2]. The decreased complexity of brain activity in AD patients has also been shown using Lempel-Ziv complexity [29].

We evaluated the ability of *ApEn* to discriminate AD patients from control subjects at the electrodes where significant differences were found using ROC curves. We obtained accuracies between 72.73% and 81.82%. Other studies have reported good accuracies when classifying AD patients and control subjects with non-linear techniques. For instance, D_2 correctly classified AD patients and controls with an accuracy of 70% [30]. Moreover, the addition of D_2 and a neural net classification procedure to linear methods improves the classification accuracy of AD up to 92% [11]. Furthermore, with a similar set of patients to the one considered in this study, we obtained accuracies between 77.27% and 90.91% with other non-linear methods, like Lempel-Ziv complexity [29], sample entropy [31] or multiscale entropy [32].

Parameters such as D_2, K-S entropy, $L1$ 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 typical 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 parameters and methods is typically very poor [19], [21]. Because dynamics 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 [23]. In fact, several properties of *ApEn* facilitate its utility for empirical time series analysis of the sort of EEGs [23]: (i) *ApEn* is nearly unaffected by noise below a *de facto* specified filter level (r), (ii) *ApEn* can be

applied to time series of 50 or more points with good reproducibility, (iii) *ApEn* is finite for stochastic, noisy deterministic and composite processes, and (iv) increasing values of *ApEn* correspond to more irregularity in the time series. Moreover, when applied to the analysis of biomedical time series, *ApEn* does not show the important drawbacks that many widely applied non-linear methods (D_2, $L1$, etc.) have.

ApEn reflects the rate of new pattern generation when the dimension decreases from $m+1$ to m. A larger value of *ApEn* means that the chance of new pattern generation is greater, so the sequence is more irregular. Given that EEG patterns reflect cortical activity (information processing) of the brain, the reduced *ApEn* in AD patients' EEG suggests deficient information processing of the cortex due to the inactivation of previously active networks [2]. Our findings are compatible with the more general hypothesis that a loss of complexity appears when biological systems become functionally impaired [33]. The EEG irregularity reduction found in some regions could be explained by a decrease of dynamical complexity of part of the brain. However, the pathophysiological implications of this decreased irregularity 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 [2].

Some limitations of our study merit consideration. First of all, the sample size was small and, as a result, 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. Moreover, the EEG changes detected with non-linear analysis techniques are not specific to AD. Among others, they have been found in several pathological states, including vascular dementia [9], Parkinson's disease [27], schizophrenia [28], epilepsy [34] and the Creutzfeld-Jakob disease [35]. Thus, although this 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.

In summary, although non-linear EEG analysis cannot yet be applied as a diagnostic tool, our findings show the possibility to analyze the dynamical behavior of the brain in AD patients and to detect significant differences with *ApEn*. Furthermore, this study shows which combination of parameters m and r is more suitable to analyze the EEG background activity in AD. Our experimental results prove the potential applications of this new family of statistics to EEG background activity characterization in AD. The EEG entropy decrease in the parietal and occipital regions in AD patients leads us to think that EEG analysis with *ApEn* could be a useful tool to increase our insight into brain dysfunction in this disease.

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REFERENCES

1. T. D. Bird, "Alzheimer's disease and other primary dementias," in *Harrison's Principles of Internal Medicine*, E. Braunwald A. S. Fauci, D. L. Kasper, S. L. Hauser, D. L. Longo, and J. L. Jameson, Eds. New York: The McGraw-Hill Companies Inc, pp. 2391–2399, 2001.
2. J. Jeong, "EEG dynamics in patients with Alzheimer's disease," *Clinical Neurophysiology*, vol. 115, pp. 1490–1505, 2004.
3. D. J. Selkoe, "Cell biology of the amyloid beta-protein precursor and the mechanism of Alzheimer's disease," *Annual Review of Cell and Biology*, vol. 10, pp. 373–403, 1994.

4. O. N. Markand, "Organic brain syndromes and dementias," in *Current Practice of Clinical Electroencephalography*, D. D. Daly and T. A. Pedley, Eds. New York, NY: Raven Press Ltd., pp. 401–423, 1990.
5. H. Kantz and T. Schreiber, *Nonlinear Time Series Analysis*. Cambridge: Cambridge University Press, 1997.
6. P. E. Rapp, "Chaos in the neurosciences: cautionary tales from the frontier," *Biologist*; vol. 40, pp. 89–94, 1993.
7. C. J. Stam, T. C. A. M. van Woerkon, and W. S. Pritchard, "Use of nonlinear EEG measures to characterize EEG changes during mental activity," *Electroencephalography and Clinical Neurophysiology*, vol. 76, pp. 214–224, 1996.
8. J. Theiler and P. E. Rapp, "Re-examination of the evidence for low-dimensional, nonlinear structure in the human electroencephalogram," *Electroencephalography and Clinical Neurophysiology*, vol. 98, pp. 213–222, 1996.
9. J. Jeong, J. H. Chae, S. Y. Kim, and S. H. Han, "Nonlinear dynamic analysis of the EEG in patients with Alzheimer's disease and vascular dementia," *Journal of Clinical Neurophysiology*, vol. 18, pp. 58–67, 2001.
10. J. Jeong, S. Y. Kim, and S. H. Han, "Non-linear dynamical analysis of the EEG in Alzheimer's disease with optimal embedding dimension," *Electroencephalography and Clinical Neurophysiology*, vol. 106, pp. 220–228, 1998.
11. W. S. Pritchard, D. W. Duke, K. L. Coburn, N. C. Moore, K. A. Tucker, M. W. Jann, and R. M. Hostetler, "EEG-based neural-net predictive classification of Alzheimer's disease versus control subjects is augmented by non-linear EEG measures," *Electroencephalography and Clinical Neurophysiology*, vol. 91, pp. 118–130, 1994.
12. J. P. Eckmann and D. Ruelle, "Fundamental limitations for estimating dimensions and Lyapunov exponents in dynamical systems," *Physica D*, vol. 56, pp. 185–187, 1992.
13. J. Jeong, J. C. Gore, and B. S. Peterson, "Mutual information analysis of the EEG in patients with Alzheimer's disease," *Clinical Neurophysiology*, vol. 112, pp. 827–835, 2001.
14. C. J. Stam, Y. van der Made, Y. A. Pijnenburg, and P. Scheltens, "EEG synchronization in mild cognitive impairment and Alzheimer's disease," *Acta Neurologica Scandinavica*, vol. 108, pp. 90–96, 2003.
15. Y. A. L. Pijnenburg, Y. vd Made, A. M. van Cappellen van Walsum, D. L. Knol, P. Scheltens and C. J. Stam, "EEG synchronization likelihood in mild cognitive impairment and Alzheimer's disease during a working memory task," *Clinical Neurophysiology*, vol. 115, pp. 1332–1339, 2004.
16. A. N. Kolmogorov, "A new metric invariant of transient dynamical systems and automorphisms in Lebesgue spaces," *Doklady Akademii Nauk SSSR*; vol. 119, pp. 861–864, 1958.
17. A. Wolf, J. B. Swift, H. L. Swinney, and J. A. Vastano, "Determining Lyapunov exponents from a time-series," *Physica D*, vol. 16, pp. 285–317, 1985.
18. S. M. Pincus and A. L. Goldberger, "Physiological time series analysis: what does regularity quantify?" *American Journal of Physiology (Heart and Circulatory Physiology)*, vol. 266, pp. H1643–H1656, 1994.
19. S. M. Pincus, "Approximate entropy as a measure of system complexity," *Proceedings of the National Academy of Sciences of the USA*, vol. 88, pp. 2297–2301, 1991.
20. M. F. Folstein, S. E. Folstein, and P. R. McHugh, "Mini-mental state. A practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, pp. 189–198, 1975.
21. S. M. Pincus and B. H. Singer, "Randomness and degrees of irregularity," *Proceedings of the National Academy of Sciences of the USA*, vol. 93, pp. 2083–2088, 1996.

22. S. M. Pincus and R. E. Kalman, “Not all (possibly) “random” sequences are created equal,” *Proceedings of the National Academy of Sciences of the USA*, vol. 94, pp. 3513–3518, 1997.
23. S. M. Pincus, “Assessing serial irregularity and its implications for health,” *Annals of the New York Academy of Sciences*, vol. 954, pp. 245–267, 2001.
24. S. M. Pincus and D. L. Keefe, “Quantification of hormone pulsatility via an approximate entropy algorithm,” *American Journal of Physiology (Endocrinology and Metabolism)*, vol. 262, pp. E741–E754, 1992.
25. D. Abásolo, R. Hornero, P. Espino, J. Poza, C. I. Sánchez, and R. de la Rosa, “Analysis of regularity in the EEG background activity of Alzheimer's disease patients with Approximate Entropy,” *Clinical Neurophysiology*, vol. 116, pp. 1826–1834, 2005.
26. M. H. Zweig and G. Campbell “Receiver-Operating Characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine,” *Clinical Chemistry*, vol. 39, pp. 561–577, 1993.
27. C. J. Stam, B. Jelles, H. A. M. Achtereekte, S. A. R. B. Rombouts, J. P. J. Slaets, and R. W. M. Keunen, “Investigation of EEG nonlinearity in dementia and Parkinson’s disease,” *Electroencephalography and Clinical Neurophysiology*, vol. 95, pp. 309–317, 1995.
28. J. Röschke, J. Fell, and P. Beckmann, “Non-linear analysis of sleep EEG data in schizophrenia: calculation of the principal Lyapunov exponent,” *Psychiatry Research*, vol. 56, pp. 257–269, 1995.
29. D. Abásolo, R. Hornero, C. Gómez, M. García, and M. López, “Analysis of EEG background activity in Alzheimer’s disease patients with Lempel-Ziv complexity and Central Tendency Measure,” *Medical Engineering and Physics*, vol. 28, pp. 315–322, 2006.
30. C. Besthorn, R. Zerfass, C. Geiger-Kabisch, H. Sattel, S. Daniel, U. Schreiter-Gasser, and H. Förstl, “Discrimination of Alzheimer’s disease and normal aging by EEG data,” *Electroencephalography and Clinical Neurophysiology*, vol. 103, pp. 241–248, 1997.
31. D. Abásolo, R. Hornero, P. Espino, D. Álvarez, and J. Poza, “Entropy analysis of the EEG background activity in Alzheimer’s disease patients,” *Physiological Measurement*, vol. 27, pp. 241–253, 2006.
32. J. Escudero, D. Abásolo, R. Hornero, P. Espino, and M. López, “Analysis of electroencephalograms in Alzheimer’s disease patients with multiscale entropy,” *Physiological Measurement*, vol. 27, pp. 1091–1106, 2006.
33. F. Ravelli and R. Antolini “Complex dynamics underlying the human electroencephalogram,” *Biological Cybernetics*, vol. 67, pp. 57–65, 1992.
34. A. Babloyantz and A. Destexhe, “Low-dimensional chaos in an instance of epilepsy,” *Proceedings of the National Academy of Sciences of the USA*, vol. 83, pp. 3513–3517, 1986.
35. A. Babloyantz and A. Destexhe, “The Creutzfeldt-Jakob disease in the hierarchy of chaotic attractors,” in *From chemical to biological organization*, M. Markus, S. Müller, and G. Nicolis, Eds. Berlin: Springer-Verlag, pp. 307–316, 1988.

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