Electroencephalogram Background Activity Characterization with Approximate Entropy and Auto Mutual Information in Alzheimer's Disease Patients

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Abstract—The aim of this study was to analyze the electroencephalogram (EEG) background activity in Alzheimer's disease (AD) with two non-linear methods: Approximate Entropy (*ApEn*) and Auto Mutual Information (*AMI*). *ApEn* quantifies the regularity in data, while *AMI* detects linear and non-linear dependencies in time series. EEGs were recorded from the 19 scalp loci of the international 10-20 system in 11 AD patients and 11 age-matched controls. *ApEn* was significantly lower in AD patients at electrodes O1, O2, P3 and P4 ($p < 0.01$). The *AMI* of the AD patients decreased significantly more slowly with time delays than the *AMI* of normal controls at electrodes T5, T6, O1, O2, P3 and P4 ($p < 0.01$). Furthermore, we observed a strong correlation between the results obtained with both non-linear methods, suggesting that the *AMI* rate of decrease can be used to estimate the regularity in time series. The decreased irregularity found in AD patients suggests that EEG analysis with *ApEn* and *AMI* could help to increase our insight into brain dysfunction in AD.

I. 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]. AD is characterized by progressive impairments in cognition and memory 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.

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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].

Since the physiological mechanisms underlying the EEG are generally non-linear, they can generate fluctuations that are not best described by linear decomposition [5]. Non-linearity in the brain is introduced even at the neuronal level [6]. Thus, the EEG appears to be an appropriate area for non-linear time series analysis [7].

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 [8]–[10]. Furthermore, AD patients also have significantly lower values of the largest Lyapunov ($L1$) exponent than controls in almost all EEG channels [8]. 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 [11]. Thus, the study of the EEG background activity with more suitable non-linear methods becomes necessary.

The present study was undertaken to examine the EEG background activity in AD with two different non-linear methods: Approximate Entropy (*ApEn*), and Auto Mutual Information (*AMI*). *ApEn* quantifies the regularity in data [12], while *AMI* detects linear and non-linear dependencies in time series [13]. We wanted to test the hypothesis that the non-linear characteristics of the EEG in AD patients would be different than in age-matched controls and to quantify the relationship between both methods.

II. MATERIAL AND METHODS

A. Subjects and EEG recording

Twenty-two subjects participated in this study. Eleven patients (5 men and 6 women; age = 72.5 ± 8.3 years, mean $\pm$ standard deviation, SD) fulfilling the criteria of probable AD were recruited from the Alzheimer's Patients' Relatives

Association of Valladolid (AFAVA) and referred to the University Hospital of Valladolid (Spain), where the EEG was recorded. All of them had undergone a thorough clinical evaluation that included clinical history, physical and neurological examinations, brain scans and a Mini-Mental State Examination (MMSE), generally accepted as a quick and simple way to evaluate cognitive function [14]. The mean MMSE score for the patients was 13.1 ± 5.9 (Mean $\pm$ SD). The control group consisted of 11 age-matched control subjects without past or present neurological disorders (7 men and 4 women; age = 72.8 ± 6.1 years, mean $\pm$ SD). The local ethics committee approved the study and all control subjects and all caregivers of the patients gave their informed consent for participation.

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 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. Afterwards, EEGs were organized in 5 second artifact-free epochs (1280 points) that were copied as ASCII files for off-line analysis on a personal computer. Furthermore, all recordings were digitally filtered with a band-pass filter with cut-off frequencies at 0.5 Hz and at 40 Hz in order to remove EMG activity prior to the computation of *ApEn* and *AMI*.

B. Approximate entropy

Approximate Entropy (*ApEn*) is a family of statistics introduced by Pincus [12] to provide a widely applicable, statistically valid formula that will distinguish data sets by a measure of regularity [12]. *ApEn* is scale invariant and model independent, it evaluates both dominant and subordinated patterns in data, and it discriminates series for which clear feature recognition is difficult [15]. Moreover, it can be applied to short time series and it is finite for stochastic, noisy deterministic and composite processes [15].

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 [15]. Given N data points from a time series $\{x(n)\} = x(1), x(2), \dots, x(N)$, one should follow these steps to

compute *ApEn* [15]:

1. Form $N-m+1$ vectors $X(1) \dots X(N-m+1)$ defined by: $X(i) = [x(i), x(i+1), \dots, x(i+m-1)]$, $i = 1 \dots N-m+1$.
2. Define the distance between $X(i)$ and $X(j)$ as:

$$d[X(i), X(j)] = \max_{k=1,2,\dots,m} |x(i+k-1) - x(j+k-1)|. \quad (1)$$
3. For a given $X(i)$, count the number of j ($j = 1 \dots N-m+1$) so that $d[X(i), X(j)] \leq r$, denoted as $N^m(i)$. Then, for $i = 1 \dots N-m+1$,

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

$C_r^m(i)$ 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 run length and find $C_r^{m+1}(i)$ and $\phi^{m+1}(r)$.
6. We define *ApEn* by:

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

Preliminary evidence suggests that applied to EEGs *ApEn* may be predictive of epileptic seizures [16], may be an effective tool to quantify the depth of anesthesia [17] and is complementary to spectral analyses of the EEG in AD [18].

Although m and r are critical in determining the outcome of *ApEn*, no guidelines exist for optimizing their values. In this pilot study, *ApEn* was estimated with $m = 1$ and $r = 0.25$ times the SD of the original data sequence. 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 [15]. These input parameters produce good statistical reproducibility in *ApEn* for time series of length $N \geq 60$, as considered herein [12].

C. Auto Mutual Information

Mutual information (*MI*) provides a measure of both the linear and non-linear statistical dependencies between two time series [13]. The *MI* between measurement x_i and measure y_i is the amount of information that the former provides about the latter. The *MI* between two measurements taken from a single time series $x(t)$ separated by time τ is called the Auto Mutual Information (*AMI*). The *AMI* estimates, on average, the degree to which $x(t+\tau)$ can be predicted from $x(t)$ and can be calculated as [13]:

$$I_{XX_\tau} = \sum_{x(t), x(t+\tau)} P_{XX_\tau}[x(t), x(t+\tau)] \cdot \ln \left\{ \frac{P_{XX_\tau}[x(t), x(t+\tau)]}{P_X[x(t)] \cdot P_{X_\tau}[x(t+\tau)]} \right\}. \quad (5)$$

$P_X[x(t)]$ is the normalized histogram of the observed $x(t)$ values distribution, while $P_{XX_\tau}[x(t), x(t+\tau)]$ is the joint probability density for the measurements of $x(t)$ and $x(t+\tau)$.

Due to the fact that *AMI* is correlated with entropy [19], it has been suggested that the rate of decrease of the *AMI* with

increasing τ is a normalized complexity measure of the time series [13]. The MI of the EEG has been used to describe the information transmission in the brain in AD [13] and in schizophrenia [20]. Moreover, it has been shown that it might be useful to predict the response to anesthesia [21].

In this pilot study, we estimated the AMI of the EEG from AD patients and control subjects for time delays between 0 and 0.5 s. The rate of decrease of the AMI was estimated using a least-squares fitting method and was computed from a time delay 0 to the first relative minimum value. This rate of decrease was used as a characterizing feature of the EEG.

D. Statistical analysis

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

The relationship between the AMI rate of decrease and $ApEn$ was examined with Pearson's linear correlation.

III. RESULTS

$ApEn$ was estimated with $m = 1$ and $r = 0.25$ times the SD of the original data sequence. The results are summarized in Table 1. $ApEn$ was lower in AD patients than in control subjects at 15 electrodes, with significant differences between both groups ($p < 0.01$) at P3, P4, O1 and O2. These results suggest that the EEG activity of AD patients is more regular than in a normal brain.

The normalized average AMI curves of the control subjects and AD patients decrease with increasing values of the time delay. Then, AMI curves show a transitory oscillation which decays as τ increases [13]. Thus, relative minimum values were located between the decreasing slope and the oscillations. The mean AMI rates of decrease for all electrodes are summarized in Table 2. These results show that, with the exception of electrode T4, the AMI decreases more slowly in AD patients, with significant differences ($p < 0.01$) at T5, T6, P3, P4, O1 and O2.

Finally, we examined the correlation between the $ApEn$ values and the rates of decrease of the AMI curves. Our results show a strong correlation between both metrics, with Pearson's correlation coefficient $\rho < -0.90$ for all electrodes with the exception of C3, C4 and F4, where $\rho < -0.85$ (p -value $\ll 0.01$). The negative correlation index is due to the nature of the AMI rates of decrease, where a more negative value is associated with higher irregularity, while $ApEn$ assigns smaller values to more regular time series. Fig. 1 represents the $ApEn$ values vs. the AMI rates of decrease at electrode T5 for control subjects and AD patients.

IV. DISCUSSION AND CONCLUSION

In this pilot study, we analyzed the EEG background activity of 11 AD patients and 11 control subjects with $ApEn$ and AMI . $ApEn$ is a family of statistics that quantifies the

TABLE I
AVERAGE $ApEn(M = 1, r = 0.25)$ VALUES FOR BOTH GROUPS OF SUBJECTS IN ALL CHANNELS. SIGNIFICANT DIFFERENCES ARE MARKED WITH AN ASTERISK.

Electrode	Control subjects (mean $\pm$ SD)	AD patients (mean $\pm$ SD)	p -value
F3	0.7378 $\pm$ 0.1821	0.6288 $\pm$ 0.1181	0.1115
F4	0.7100 $\pm$ 0.2028	0.6933 $\pm$ 0.1371	0.8242
F7	0.7732 $\pm$ 0.2072	0.7349 $\pm$ 0.1634	0.6355
F8	0.7867 $\pm$ 0.1775	0.7309 $\pm$ 0.1563	0.4426
Fp1	0.7182 $\pm$ 0.1649	0.5641 $\pm$ 0.2006	0.0631
Fp2	0.6994 $\pm$ 0.2194	0.5745 $\pm$ 0.1363	0.1243
T3	0.9580 $\pm$ 0.2869	0.9236 $\pm$ 0.2472	0.7663
T4	0.9296 $\pm$ 0.2485	0.9342 $\pm$ 0.3186	0.9701
T5	0.9125 $\pm$ 0.1953	0.6936 $\pm$ 0.2081	0.0193
T6	0.8976 $\pm$ 0.2018	0.6914 $\pm$ 0.2179	0.0322
C3	0.8363 $\pm$ 0.1670	0.7291 $\pm$ 0.1954	0.1820
C4	0.8490 $\pm$ 0.1384	0.7703 $\pm$ 0.2150	0.3198
P3*	0.8599 $\pm$ 0.1331	0.6088 $\pm$ 0.1817	0.0014
P4*	0.8644 $\pm$ 0.1320	0.6423 $\pm$ 0.1753	0.0031
O1*	0.9714 $\pm$ 0.1801	0.6989 $\pm$ 0.1939	0.0027
O2*	0.9357 $\pm$ 0.2051	0.6867 $\pm$ 0.1961	0.0086

TABLE II
AVERAGE AMI RATES OF DECREASE FOR BOTH GROUPS OF SUBJECTS IN ALL CHANNELS. SIGNIFICANT DIFFERENCES ARE MARKED WITH AN ASTERISK.

Electrode	Control subjects (mean $\pm$ SD)	AD patients (mean $\pm$ SD)	p -value
F3	-12.46 $\pm$ 3.83	-9.88 $\pm$ 1.73	0.0560
F4	-12.72 $\pm$ 2.90	-10.69 $\pm$ 2.43	0.0894
F7	-12.64 $\pm$ 3.81	-11.62 $\pm$ 3.53	0.5244
F8	-13.33 $\pm$ 3.53	-11.70 $\pm$ 3.45	0.2855
Fp1	-12.54 $\pm$ 3.34	-9.09 $\pm$ 2.34	0.0108
Fp2	-11.87 $\pm$ 3.72	-8.49 $\pm$ 2.20	0.0174
T3	-15.15 $\pm$ 4.64	-14.62 $\pm$ 5.12	0.8029
T4	-14.97 $\pm$ 3.94	-15.19 $\pm$ 6.60	0.9247
T5*	-14.83 $\pm$ 3.51	-9.68 $\pm$ 2.92	0.0013
T6*	-14.43 $\pm$ 3.33	-10.39 $\pm$ 3.33	0.0099
C3	-13.91 $\pm$ 3.02	-11.98 $\pm$ 3.17	0.1595
C4	-14.25 $\pm$ 3.26	-12.63 $\pm$ 3.63	0.2856
P3*	-14.48 $\pm$ 2.84	-9.43 $\pm$ 2.70	0.0004
P4*	-14.66 $\pm$ 2.72	-9.98 $\pm$ 2.64	0.0006
O1*	-15.61 $\pm$ 3.45	-10.28 $\pm$ 3.25	0.0013
O2*	-14.57 $\pm$ 3.65	-10.15 $\pm$ 3.24	0.0070

regularity in time series, with increasing values corresponding to more irregularity [15]. AMI estimates the degree to which $x(t + \tau)$ can be predicted from $x(t)$ [13]. Both methods do not require a large number of data points to be reliably estimated and can be applied to non-stationary time series [13], [15]. Thus, they are much better suited for EEG analysis than traditional non-linear techniques as $L1$ or D_2 .

We have found that $ApEn$ was significantly lower in the AD patients' EEG at electrodes P3, P4, O1 and O2 ($p < 0.01$). Furthermore, our study shows that the AMI decreases more slowly with τ in AD patients. We have estimated the AMI rate of decrease to characterize the EEG, and we have found significant differences between both groups at electrodes T5, T6, P3, P4, O1 and O2 ($p < 0.01$). Moreover, our study reveals that the absolute values of the AMI rate of decrease are strongly correlated with $ApEn$. Fig. 1 shows an example where the strong correlation between both metrics at electrode T5 becomes clear. The negative relationship is due to the fact that, while $ApEn$ values are positive and

Fig. 1. $ApEn$ values versus the AMI rates of decrease for AD patients (circumferences) and control subjects (asterisks) at electrode T5. Pearson's correlation index is $\rho = -0.94487$. The straight line that fits the data in a least-squares sense has been plotted.

larger in more irregular time series, the more negative AMI rates of decrease are associated with higher irregularity. Some authors have chosen to quantify complexity with the AMI rate of decrease [13]. However, given the fact that $ApEn$ is a regularity estimator, this strong correlation suggests that the AMI rate of decrease might be used to quantify the regularity of a time series instead of its complexity. A complexity measure should vanish for both completely regular and completely random system [22], something that does not happen with $ApEn$ [23].

Our results suggest that the EEG background activity in AD patients is more regular than in control subjects, especially in the parietal and occipital regions, and are consistent with previous studies that have shown EEG changes in AD with non-linear techniques [8]–[10], [13], [18]. The increased regularity in the EEG of AD patients could be explained by a decrease of dynamical complexity of part of the brain. However, the implications of this decreased EEG 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 [2].

Although our results indicate that $ApEn$ and AMI could be useful in AD diagnosis, some limitations must be mentioned. Firstly, the sample size was small. To prove the usefulness of these techniques as an AD diagnostic tool, this approach should be extended on a much larger patient population. Moreover, the detected regularity increase in the EEG is not specific to AD and further work must be carried out to examine non-linear EEG activity in other types of dementia.

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