

Analysis of Spontaneous EEG Activity in Alzheimer's Disease Using Cross-Sample Entropy and Graph Theory

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Abstract— The aim of this pilot study was to analyze spontaneous electroencephalography (EEG) activity in Alzheimer's disease (AD) by means of Cross-Sample Entropy (*Cross-SampEn*) and two local measures derived from graph theory: clustering coefficient (*CC*) and characteristic path length (*PL*). Five minutes of EEG activity were recorded from 37 patients with dementia due to AD and 29 elderly controls. Our results showed that *Cross-SampEn* values were lower in the AD group than in the control one for all the interactions among EEG channels. This finding indicates that EEG activity in AD is characterized by a lower statistical dissimilarity among channels. Significant differences were found mainly for fronto-central interactions ($p < 0.01$, permutation test). Additionally, the application of graph theory measures revealed diverse neural network changes, i.e. lower *CC* and higher *PL* values in AD group, leading to a less efficient brain organization. This study suggests the usefulness of our approach to provide further insights into the underlying brain dynamics associated with AD.

I. INTRODUCTION

Alzheimer's disease (AD) is a primary degenerative dementia, which gradually destroys brain cells. The number of people with dementia increases exponentially with increasing age. AD affects 1% of population under 60 years but reaches 30% for people over 85 years. Besides, due to the increase in average life expectancy during the 21st century, it is expected that dementia will affect 81.1 million people by 2040 [1]. Thus, AD is becoming a key public-healthcare and economic problem.

Pathologically, AD is characterized by the deposition of amyloid beta-peptide as insoluble extracellular plaques and intracellular tau aggregation [2]. Currently, a definite diagnosis of AD requires examination of brain tissue at autopsy. For this reason, physicians can really only make a diagnosis of probable AD. Clinical diagnosis usually includes medical history, neurological examination, blood tests, and neuroimaging studies. Nowadays, electroencephalography

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(EEG) is not always used in AD diagnosis, in spite of its potential to characterize neural dynamics [3]. EEG is a non-invasive technique to measure the electromagnetic brain activity [4]. It allows the assessment of the spatio-temporal patterns of neural activity and their interactions in the time range of milliseconds [5]. The EEG reflects not only brain oscillation activity but also the underlying associated neural dynamics [6]. As AD affects the cerebral cortex areas, EEG is a useful technique to understand the neural mechanisms of this disorder.

For the analysis of EEG activity in AD, spectral techniques are the most extended option, due to their simplicity and ease of clinical interpretation. Spectral analyses seem to discriminate AD patients from control subjects through an increased brain activity in lower frequency bands associated with AD [7]. From another point of view, non-linear analysis techniques have been widely used since the mid-90s [8]. Several non-linear analysis methods have suggested that AD elicits a complexity decrease in spontaneous brain activity (using Lempel-Ziv complexity or fractal dimension) and an increase of regularity (using approximate entropy and sample entropy) [9-10]. All these methods (both spectral and non-linear) measure local activation patterns in individual sensors. However, it has become clear that simple activation studies are no longer sufficient for AD characterization [11]. For this reason, graph theory has been introduced in cognitive neuroscience to overcome the limitations of the aforementioned analyses. In this regard, the application of graph theory concepts can be used to gain more insight into the AD pathophysiological processes [12].

In this study, EEG activity has been analyzed in 37 patients with dementia due to AD and 29 control subjects using Cross-Sample Entropy (*Cross-SampEn*) and two local measures derived from graph theory: clustering coefficient (*CC*) and characteristic path length (*PL*). Our aim is to characterize the neural mechanisms in AD.

II. MATERIALS

A. Subjects

EEG data were acquired from 66 subjects. The AD group was formed by thirty-seven patients with mild/moderate dementia due to AD, diagnosed according to the clinical criteria of the National Institute on Aging and Alzheimer's Association (NIA-AA). Twenty-nine elderly subjects without cognitive impairments and with no history of neurological or psychiatric disorders comprised the control group. Table 1 shows socio-demographic and clinical data for both groups.

TABLE I. SOCIO-DEMOGRAPHIC AND CLINICAL DATA FOR EACH GROUP

	AD group	Control group
Number of subjects	37	29
Age (years) (Mean \pm SD)	79.2 \pm 6.9	76.6 \pm 7.2
Gender (Male:Female)	13:24	9:20
MMSE^a (Mean \pm SD)	18.7 \pm 6.2	28.9 \pm 1.3

^a MMSE: Mini-mental State Examination

All participants and patients' caregivers were informed about the research background and the study protocol. Moreover, all of them gave their written informed consent to be included in the study. The Ethics Committee at the "Hospital Universitario Río Hortega" (Valladolid, Spain) endorsed the study protocol, according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

B. EEG recording

EEG activity was acquired with a 19-channel EEG system (XLTEK®, Natus Medical). For each subject, five minutes of resting-state EEG activity were recorded at a sampling frequency of 200 Hz from the 19 following electrodes: Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1 and O2. EEG data were then digitally filtered between 1 and 40 Hz. Finally, 27.7 \pm 8.4 (mean \pm standard deviation, SD) artifact-free 5-s length epochs per channel and subject were selected by visual inspection.

III. METHODS

A. Cross Sample Entropy (Cross-SampEn)

Cross-SampEn is a nonlinear measure that allows assessing the degree of similarity of two time series [13]. It was proposed by Richman and Moorman to overcome some drawbacks of a related algorithm called Cross-Approximate Entropy (*Cross-ApEn*). Firstly, *Cross-SampEn* remains relatively consistent for conditions where *Cross-ApEn* does not. Secondly, *Cross-ApEn* is not always defined. *Cross-SampEn* solves this problem. Finally, there is other important difference between these two algorithms: whereas *Cross-ApEn* analysis exhibits direction dependence (i.e. it is an asymmetric method), *Cross-SampEn* is a direction independent measure.

To compute *Cross-SampEn*, a run length m and a tolerance window r must be set. Given two time series, $u(i)$ and $v(i)$, *Cross-SampEn* measures, within tolerance r , the frequency of v -patterns similar to a given u -pattern of length m . Although a right choice of m and r are important to calculate *Cross-SampEn*, no guidelines exist to optimize their values. However, values of m equal to 1 or 2, and r between 0.1 and 0.25 have been suggested [14]. In this pilot study, we have specified values of $m = 1$ and $r = 0.2$. The detailed algorithm to calculate the *Cross-SampEn* between two signals $u(i)$ and $v(i)$ is the following [13, 15]:

- 1) Normalize $u(i)$ and $v(i)$. The normalized time series $u^*(i)$ and $v^*(i)$ are:

$$u^*(i) = [u(i) - \text{mean}(u)] / \text{SD}(u) \quad (1)$$

$$v^*(i) = [v(i) - \text{mean}(v)] / \text{SD}(v) \quad (2)$$

- 2) Form the vector sequences:

$$x_m(i) = [u^*(i), u^*(i+1), \dots, u^*(i+m-1)], \quad 1 \leq i \leq N-m \quad (3)$$

$$y_m(j) = [v^*(j), v^*(j+1), \dots, v^*(j+m-1)], \quad 1 \leq j \leq N-m. \quad (4)$$

- 3) Define the distance between the vector sequences $x_m(i)$ and $y_m(j)$ as:

$$d[x_m(i), y_m(j)] = \max_{k=0,1,\dots,m-1} |u^*(i+k) - v^*(j+k)|. \quad (5)$$

- 4) For each $x_m(i)$, count the number of j ($j=1,2,\dots,N-m$) so that $d[x_m(i), y_m(j)] \leq r$, denoted as $b_i^m(r)$. Then, for $i=1,2,\dots,N-m$, set:

$$B_i^m(r)(v\|u) = \frac{b_i^m(r)}{N-m}. \quad (6)$$

$B_i^m(r)(v\|u)$ is the probability that any $y_m(j)$ is within r of $x_m(i)$.

- 5) Define $B^m(r)(v\|u)$ as:

$$B^m(r)(v\|u) = \frac{1}{N-m} \sum_{i=1}^{N-m} B_i^m(r)(v\|u). \quad (7)$$

- 6) Similarly, define $A_i^m(r)(v\|u)$ as $1/(N-m)$ times the number of j ($j=1,2,\dots,N-m$), such the distance between $x_{m+1}(i)$ and $y_{m+1}(j)$ is less than or equal to r . Then, calculate:

$$A^m(r)(v\|u) = \frac{1}{N-m} \sum_{i=1}^{N-m} A_i^m(r)(v\|u). \quad (8)$$

$B^m(r)(v\|u)$ is the probability that two templates matches for m points, whereas $A^m(r)(v\|u)$ is the probability that two templates matches for $m+1$ points.

- 7) Finally, *Cross-SampEn* is defined as:

$$\text{Cross-SampEn}(m, r, N)(v\|u) = -\ln \left[\frac{A^m(r)(v\|u)}{B^m(r)(v\|u)} \right]. \quad (9)$$

In this study, *Cross-SampEn* has been computed for all pairwise combinations of EEG channels. After the averaging process over all artifact-free epochs, a 19×19 *Cross-SampEn* matrix per subject was obtained.

B. Graph Theory

Graph theory is the scientific study of graphs or networks. A graph is a set of nodes (or vertices) and the corresponding set of edges (or connections), defined as the connectivity/similarity values among nodes [16]. In our study, a network with $N = 19$ nodes (corresponding to the aforementioned 19 EEG electrodes) was analyzed. The edge between two vertices k and l takes the *Cross-SampEn* value between channels k and l . The edge weight between these two vertices k and l is denoted as w_{kl} . A graph can be characterized using various network parameters. In this study, CC and PL were calculated for each node.

We can define the CC of a node k , CC_k , as the probability that other nodes l , that are connected to node k , will be also connected to each other [17]:

$$CC_k = \frac{\sum_{\substack{p \neq k \\ q \neq p}} w_{kp} w_{kq} w_{pq}}{\sum_{\substack{p \neq k \\ q \neq p}} w_{kp} w_{kq}}. \quad (10)$$

On the other hand, PL of node k , PL_k , is calculated as the average minimal travel distance d_{kl} between node k and all nodes l [18]:

$$PL_k = \frac{\sum_{l \neq k} d_{kl}}{N-1}, \quad (11)$$

where d_{kl} is the shortest weighted distance between nodes k and l in the graph and N is the number of nodes of the network ($N=19$).

C. Statistical analysis

Statistical comparison between groups was performed by means of multiple comparisons nonparametric permutation test. It allows achieving a strong control over type I error in situations in which the multiplicity of testing must be taken into account, as in this case.

IV. RESULTS

Firstly, *Cross-SampEn* measure was applied to the EEG data with parameter values of $m = 1$ and $r = 0.2$. Fig. 1a illustrates entropy values for both groups. This figure shows that *Cross-SampEn* values were higher in the control group than in AD group for all EEG channels combinations. This finding suggests that dementia due to AD is characterized by a higher degree of similarity among channels. Right panel of Fig. 1a summarized statistical results (it is important to note

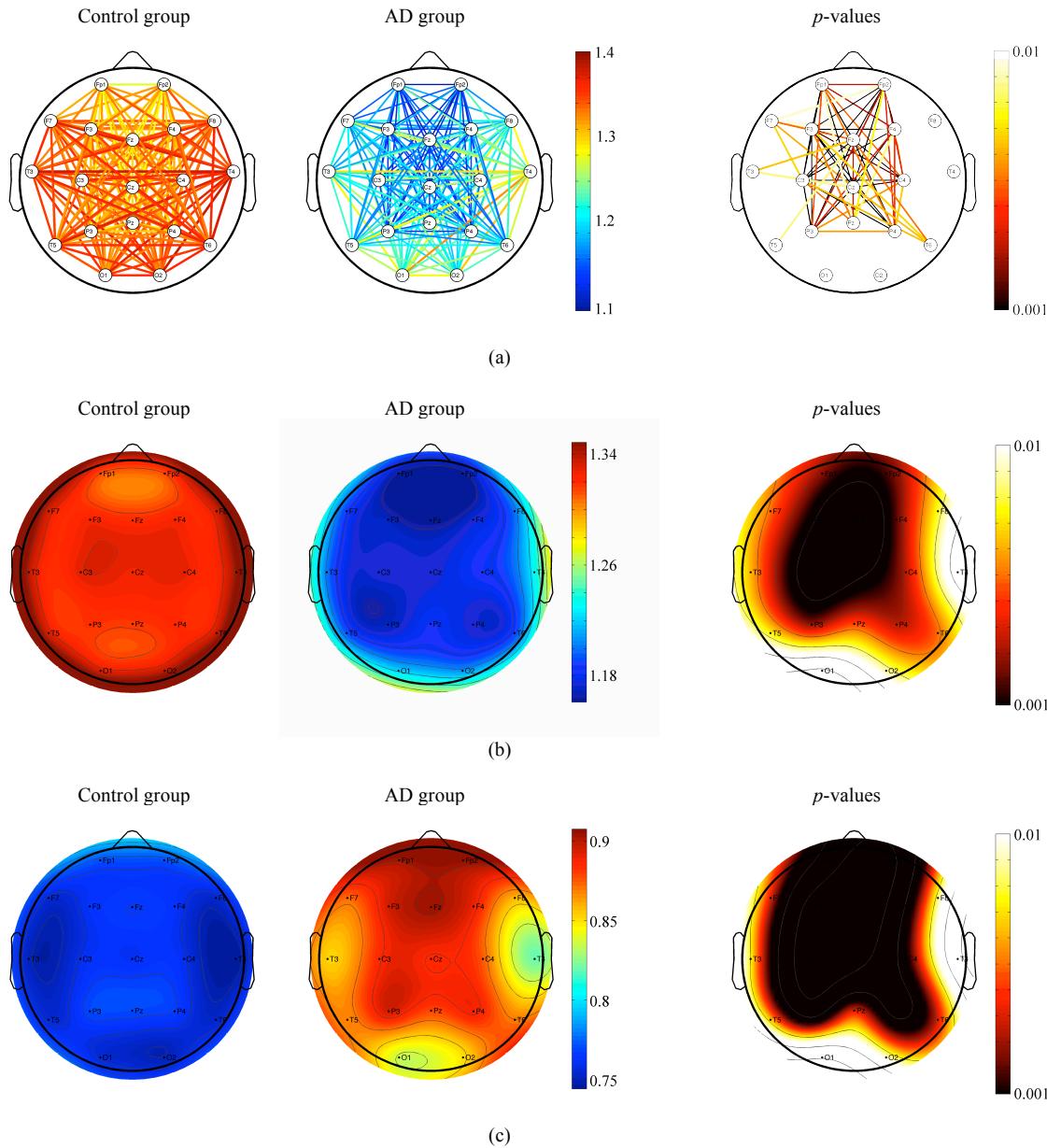


Figure 1. EEG layouts showing the distribution of mean values for each group (Controls and AD patients) and the corresponding p -values: (a) Cross-SampEn measure; (b) Clustering coefficient; (c) Characteristic path length.

that only significant differences between groups are displayed).

Secondly, *CC* and *PL* measures were calculated from *Cross-SampEn* values. As expected, our results revealed that AD is associated with lower *CC* in comparison with controls. On the other hand, the patients group exhibited higher values of *PL* than the control group. Differences were statistically significant ($p < 0.01$, nonparametric permutation test) with both parameters in all EEG channels, with the exception of T4 and O1.

V. DISCUSSION AND CONCLUSION

In this pilot study, EEG activity was analyzed from 37 patients with dementia due to AD and 29 elderly control subjects by means of *Cross-SampEn*, *CC* and *PL*. Our main goal was to characterize the neural mechanisms in AD.

Cross-SampEn results revealed that AD patients exhibit a higher degree of similarity among channels than controls. These findings agree with previous studies. For instance, Jeong *et al.* [19] reported lower values of cross-mutual information in AD subjects than in controls, mainly over frontal and antero-temporal regions. Koenig *et al.* [20] analyzed a large EEG database of control subjects and patients with varying degrees of cognitive decline or AD using global field synchronization. Their results showed decreased synchronization values in alpha, beta, and gamma frequency bands [20]. All these studies support the notion that AD is associated with a loss of functional connectivity.

Graph theory results showed lower *CC* and higher *PL* values in AD group in comparison with the control one. As *CC* provides a measure of the node strength, our study indicates that functional brain networks in AD are characterized by a diminished strength. On the other hand, our *PL* results suggest that the different brain areas are worse connected in AD group. These findings partially agree with previous studies. Using synchronization likelihood and unweighted graphs, de Haan *et al.* [12] found a significant decrease of *CC* in the lower alpha and beta bands in AD group, but also diminished *PL* values in the lower alpha and gamma bands. The main finding of an fMRI study is that brain networks in AD are characterized by lower *CC* values but similar *PL* values in comparison with controls [21]. These researches suggest that AD is associated with less efficient information exchange between brain areas [12].

Some limitations of our research work merit consideration. Firstly, the sample size was limited to 66 subjects. In addition to this, only AD patients and controls took part in this study. Future efforts will be focused to increase the number of subjects, as well as to include mild cognitive impairment subjects, as this condition is considered a prodromal stage of AD. Finally, *CC* and *PL* are not the only measures to characterize brain networks, so other graph theory parameters could provide complementary information.

In sum, our study leads us to conclude that spontaneous EEG activity in AD patients is accompanied by diverse neural network changes. This study suggests the usefulness of our approach (combination of *Cross-SampEn*, *CC* and *PL*) to provide further insights into the underlying brain dynamics associated with AD.

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