Analysis of Magnetoencephalography Recordings from Alzheimer's Disease Patients Using Embedding Entropies

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***Abstract*— The aim of this study was to examine the magnetoencephalography (MEG) background activity in Alzheimer's disease (AD) using three embedding entropies: approximate entropy (*ApEn*), sample entropy (*SampEn*), and fuzzy entropy (*FuzzyEn*). These three methods measure the time series regularity. Five minutes of recording were acquired with a 148-channel whole-head magnetometer from 36 AD patients and 24 elderly control subjects. Our results showed that MEG activity was more regular in AD patients than in controls. Additionally, *FuzzyEn* revealed statistically significant differences between the two groups ($p < 0.01$, Bonferroni-corrected Mann-Whitney U-test), while *ApEn* and *SampEn* did not. The better discriminating results of *FuzzyEn* in comparison with the other entropy algorithms suggest that it is more efficient for the characterization of MEG activity in AD.**

I. Introduction

Alzheimer's disease (AD) is a neurological disorder of unknown etiology that gradually destroys brain cells. AD prevalence is rising in line with aging population, reaching 30% of the people over 85 years [1]. A definite diagnosis is only possible by autopsy after death. Clinical criteria for AD diagnosis include cognitive tests, medical history studies, physical and neurological evaluation, and neuroimaging techniques. Nowadays, magnetoencephalography (MEG) is not used in AD diagnosis, in spite of its potential to characterize neural dynamics. MEG is a neuroimaging technique used to measure the very small changes in the electromagnetic brain activity. As the magnetic fields due to neural activity are extremely weak, an array of very sensitive sensors (SQUIDs, superconducting quantum interference devices), positioned over the scalp, is needed. Additionally, interference suppression systems and magnetic shielding are mandatory [2]. On the other hand, MEG offers some advantages over electroencephalography (EEG). MEG is reference-free and is less affected by the volume conduction than EEG [3].

During the last years, several studies analyzed the MEG activity in AD using signal processing techniques. Spectral analyses suggested that AD is associated with an increased MEG activity in lower frequency bands and a decreased one in higher ones in comparison with control subjects [4]. Studies analyzing functional connectivity revealed a general loss of coherence in all frequency bands [5]. On the other hand, nonlinear measures identified that the spontaneous MEG activity is less complex, less predictable, and more regular in patients than in control subjects [6–8].

In this study, we have examined the MEG background activity in AD using three different measures of entropy: approximate entropy (*ApEn*), sample entropy (*SampEn*), and fuzzy entropy (*FuzzyEn*). Entropy is a concept addressing randomness and predictability, with greater entropy often associated with more randomness and less system order [9]. Applied to time series, these three measures quantify the signal regularity. Our purpose is: (i) to check the hypothesis that entropy values from MEG activity would be different in AD patients and elderly controls, and (ii) to test which measure is more appropriate to discriminate between these two groups.

II. Materials and Methods

A. Subjects

MEG data were acquired from 60 subjects: 36 patients with probable AD and 24 elderly controls. The cognitive and functional deficits were screened in both groups with the mini-mental state examination (MMSE) and the functional assessment staging (FAST).

MEGs were recorded from thirty-six AD patients (12 men and 24 women, age = 74.1 ± 6.9 years, mean ± standard deviation), who were recruited from the 'Asociación de Familiares de Enfermos de Alzheimer' and the Geriatric Unit of the 'Hospital Clínico Universitario San Carlos' (Madrid, Spain). All patients fulfilled the criteria for probable AD, according to the clinical guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association [10]. Patients were free of significant medical, neurological and psychiatric diseases other than AD. They obtained mean scores of 18.1 ± 3.4 and 4.2 ± 0.4 (mean ± standard deviation) on MMSE and FAST, respectively.

The control group consisted of twenty-four subjects without past or present neurological disorders (9 men and 15 women; age = 71.7 ± 6.5 years; MMSE score = 28.9 ± 1.2 points; FAST score = 1.7 ± 0.5 points; mean ± standard

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deviation). Differences in the mean age or gender of both populations were not statistically significant. The local ethics committee approved this study. All control subjects and all caregivers of the patients gave their informed consent for the participation in the current study.

B. MEG recording

MEG signals were acquired with a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) placed in a magnetically shielded room at the MEG Center Dr. Pérez-Modrego (Spain). The subjects lay comfortably on a patient bed, in a relaxed state and with their eyes closed, in order to reduce the presence of artifacts in the recordings. Five minutes of MEG data were acquired from each subject at a sampling frequency of 678.17 Hz. A process of down-sampling by a factor of four was carried out, resulting a sampling rate of 169.55 Hz. Data were digitally filtered using a 1-65 Hz band-pass filter and a 50 Hz notch filter. Both visual inspection and independent component analysis (ICA) were performed to minimize the presence of oculographic, cardiographic and myographic artifacts. All artifact-free epochs of 5 s (848 data points) were selected for further analyses.

C. Entropy measures

Approximate entropy (*ApEn*), sample entropy (*SampEn*) and fuzzy entropy (*FuzzyEn*) are embedding entropies that quantify the regularity of a time series, notwithstanding its stochastic or deterministic origin [11–13]. Embedding entropies provide information about how a signal fluctuates with time by comparing the time series with a delayed version of itself [14]. *ApEn*, *SampEn* and *FuzzyEn* assign a non-negative number to a sequence, with larger values corresponding to greater apparent process randomness or serial irregularity, and smaller values corresponding to more instances of recognizable features or patterns in the data. *ApEn* algorithm was proposed by Pincus for the analysis of short and noisy data sets [11]. For this reason, it has been widely used to study the irregularity of several kinds of biomedical signals. Nevertheless, *ApEn* overestimates the similarity and is thus biased. To solve this drawback, Richman and Moorman introduced *SampEn* [12]. It is largely independent of the signal length and displays relative consistency under circumstances where *ApEn* does not [12]. However, the similarity definition of vectors in both *ApEn* and *SampEn* is based on Heaviside function. Due to inherent imperfections of this function, some problems exist in the validity of these entropies definitions [15]. To overcome these drawbacks, *FuzzyEn* was proposed by Chen *et al.* [13]. Previous results showed that it is a more accurate irregularity measure [15]. To compute *ApEn* and *SampEn*, two parameters must be specified: a tolerance window r and a run length m [11, 12] For *FuzzyEn* algorithm, three input parameters are needed: the width (r) and the gradient (n) of the boundary of the exponential function, and a run length m [13, 15].

1) ApEn algorithm

The algorithm used to compute the *ApEn* of a signal $\{x(n)\} = x(1), x(2),\ldots, x(N)$ is as follows [11]:

1) Form $N - m + 1$ vectors $X_m(i)$ defined by $X_m(i) = [x(i), x(i + 1),\ldots, x(i + m - 1)]$, $i = 1,\ldots, N - m + 1$.
2) Define the distance, $d_{ij}^{\,m}$, between two of these vectors $X_m(i)$ and $X_m(j)$ as the maximum difference of their corresponding scalar components.
3) For a given $X_m(i)$, let $N_m(i)$ denote the number of j ($j = 1,\ldots, N - m + 1$) so that $d_{ij}^{\,m} \le r$. Thus, for $i = 1,\ldots, N - m + 1$:
$$C_r^m(i) = \frac{N^m(i)}{N - m + 1}. \quad (1)$$
$C_r^m(i)$ measures, within a tolerance r, the regularity or 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:
$$\varphi^m(r) = \frac{1}{N - m + 1}\sum_{i=1}^{N-m+1} \ln C_r^m(i). \quad (2)$$
5) Increase the dimension to $m + 1$ and repeat previous steps in order to obtain $C_r^{m+1}(i)$ and $\varphi^{m+1}(r)$.
6) For finite datasets, *ApEn* is estimated by the statistic:
$$ApEn(m, r, N) = \varphi^m(r) - \varphi^{m+1}(r). \quad (3)$$

2) SampEn algorithm

The algorithm used to compute the *SampEn* of a signal $\{x(n)\} = x(1), x(2),\ldots, x(N)$ is as follows [12]:

1) Form $N - m + 1$ vectors $X_m(i)$ defined by $X_m(i) = [x(i), x(i + 1),\ldots, x(i + m - 1)]$, $i = 1,\ldots, N - m + 1$.
2) Define the distance, $d_{ij}^{\,m}$, between two of these vectors $X_m(i)$ and $X_m(j)$ as the maximum difference of their corresponding scalar components.
3) Define $B_i^m(r)$ as $1/(N - m - 1)$ times the number of j ($1 \le j \le N - m; j \ne i$), so that $d_{ij}^{\,m} \le r$. Then, set $B_m(r)$ as:
$$B_m(r) = \frac{1}{N - m}\sum_{i=1}^{N-m} B_i^m(r). \quad (4)$$
4) Increase the dimension to $m + 1$ and calculate $A_i^m(r)$ as $1/(N - m - 1)$ times the number of j ($1 \le j \le N - m$; $j \ne i$), so that $d_{ij}^{\,m+1} \le r$. Set $A_m(r)$ as:
$$A_m(r) = \frac{1}{N - m}\sum_{i=1}^{N-m} A_i^m(r). \quad (5)$$
5) For finite datasets, *SampEn* is estimated by the statistic:
$$SampEn(m, r, N) = -\ln\frac{A_m(r)}{B_m(r)}. \quad (6)$$

3) FuzzyEn algorithm

The algorithm used to compute the *FuzzyEn* of a signal $\{x(n)\} = x(1), x(2),\ldots, x(N)$ is as follows [13]:

1) Form $N - m + 1$ vectors $X_m(i)$ defined by $X_m(i) = [x(i), x(i + 1),\ldots, x(i + m - 1)] - x_0(i)$, where $x_0(i)$ is given by:
$$x_0(i) = \frac{1}{m}\sum_{j=0}^{m-1} x(i + j). \quad (7)$$
2) Define the distance, $d_{ij}^{\,m}$, between two of these vectors $X_m(i)$ and $X_m(j)$ as the maximum difference of their corresponding scalar components.

3) Calculate the similarity degree, D_{ij}^{m}, of $X_m(i)$ and $X_m(j)$ through a fuzzy function $\mu(d_{ij}^{m},n,r)$. In this study, the exponential function was used:

$$D_{ij}^{m}(n,r) = \mu\left(d_{ij}^{m},n,r\right) = \exp\left(-\left(d_{ij}^{m}\right)^{n}/r\right). \quad (8)$$

4) Define the function ϕ^{m} as follows:

$$\phi^{m}(n,r) = \frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m-1}\sum_{j=1,j\neq i}^{N-m}D_{ij}^{m}\right). \quad (9)$$

5) Increase the dimension to $m + 1$ and repeat previous steps in order to obtain ϕ^{m+1}.

6) For finite datasets, *FuzzyEn* is estimated by the statistic:

$$FuzzyEn(m,n,r,N) = \ln\phi^{m}(n,r) - \ln\phi^{m+1}(n,r). \quad (10)$$

III. Results

ApEn, *SampEn* and *FuzzyEn* algorithms were applied to MEG signals acquired at 148 locations. For *ApEn* and *SampEn*, the same combination of parameters was used: m = 2 and r = 0.2 times the standard deviation of the original time series. On the other hand, *FuzzyEn* was applied with parameter values of m = 2, n = 2, and r = 0.2. Figure 1 summarizes the averaged entropy values at each MEG channel for both AD and control groups. This figure shows that entropy values were lower in AD patients than in controls, which suggests that this neurological disorder is accompanied by a regularity increase of MEG activity.

In a first step, Mann-Whitney U-test was used to asses the statistical differences between patients and control subjects. For this analysis, the results at the 148 MEG channels were

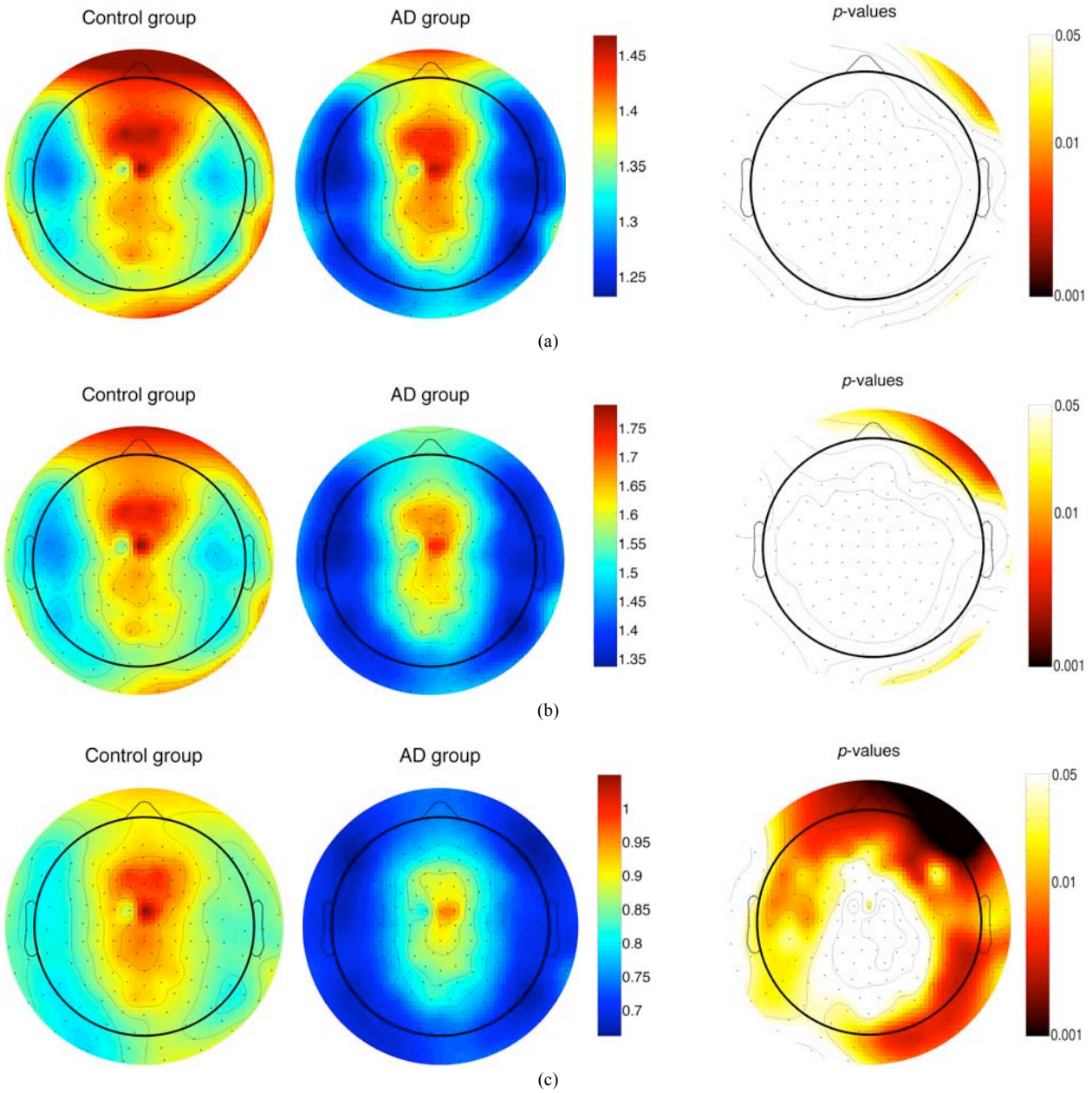

Figure 1. Sensor layout showing the distribution of the mean entropy values for control subjects and AD patients, and the corresponding *p*-values: (a) Approximate entropy; (b) Sample entropy; (c) Fuzzy entropy.

averaged. We obtained *p*-values of 0.4236, 0.1689 and 0.0036 for *ApEn*, *SampEn* and *FuzzyEn*, respectively (Bonferroni-corrected Mann-Whitney U-test).

Additionally, statistical analyses at sensor-level were performed using a multiple comparison nonparametric permutation test [16]. This test lets to control type I error when the multiplicity of testing must be taken into account (e.g. 148 sensors). Right column of figure 1 illustrates that just a few channels (placed in frontal, right lateral and posterior regions) revealed significant differences using *ApEn* and *SampEn* algorithms. On the other hand, *FuzzyEn* was able to differentiate AD patients from controls at several sensor locations, mainly placed at frontal and temporal brain regions.

IV. Discussion and conclusions

In this study, we analyzed the MEG background activity from 36 AD patients and 24 control subjects by means of *ApEn*, *SampEn* and *FuzzyEn*. Our purpose was to check the hypothesis that MEG background activity was different in these groups. Our results revealed that AD patients have lower entropy values than controls, indicating a regularity increase of MEG activity associated with the disease. The main differences between groups were found in frontal and temporal brain areas. This finding may reflect the major loss of synapses occurred in AD at these regions [17]. Our results agree with previous EEG and MEG studies that used different embedding entropies to characterize the brain activity in AD [7–9].

Additionally, statistically significant differences were found with *FuzzyEn* (*p*-value = 0.0036, Bonferroni-corrected Mann-Whitney U-test). This fact suggests that *FuzzyEn* is a more suitable measure for MEG characterization in AD than *ApEn* and *SampEn*. Chen *et al*. [13] applied these three related measures to electromyography signals in order to compare their performance on measuring signal regularity. For this purpose, recordings from four different motions (hand grasping, hand opening, forearm supination, and forearm pronation) were analyzed. *SampEn* showed a better discrimination than *ApEn*, with the boundaries among motions much more apparent. In addition to this, *FuzzyEn* resulted in the best characterization results [13]. Our results go in the same direction, as the lowest *p*-value was achieved for *FuzzyEn* and the highest one for *ApEn*. This may be due to the fact that *FuzzyEn* uses an exponential function to bound vectors similarity. This fuzzy function is characterized by no rigid boundary, instead of the Heaviside function used in *ApEn* and *SampEn* algorithms. However, it is noteworthy that *FuzzyEn* approach is computationally more demanding.

In this study, some limitations must be considered. Firstly, the detected regularity increase is not specific to AD, appearing in other brain disorders. Additionally, other entropy measures, such as spectral entropy, permutation entropy or conditional entropy, may provide complementary results. Finally, our results do not show if these measures can detect a gradation of the disease process. Future efforts will be focussed to increase the MEG database, as well as to extend the methodology to other diseases. Mild cognitive impairment group is particularly interesting, as this disorder is considered a prodromal phase of AD.

In sum, our study leads us to conclude that MEG background activity in AD patients is more regular than in controls. *FuzzyEn* results showed significant differences between AD patients and controls, indicating an abnormal type of dynamics associated with AD. This irregularity reduction may be associated with the deficiencies in information processing suffered by AD patients.

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