Analysis of MEG recordings from Alzheimer's disease patients with sample and multiscale entropies

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***Abstract*—Alzheimer's disease (AD) is one of the most prominent neurodegenerative disorders. The aim of this study is to analyze the magnetoencephalogram (MEG) background activity in AD patients using sample entropy (*SampEn*) and multiscale entropy (*MSE*). The former quantifies the signal regularity, while the latter is a complexity measure. These concepts, irregularity and complexity, are linked although the relationship is not straightforward. Five minutes of recording were acquired with a 148-channel whole-head magnetometer in 20 patients with probable AD and 21 control subjects. Our results show that MEG recordings are less complex and more regular in AD patients than in control subjects. Significant differences between both groups were found in some MEG channels with both methods ($p < 0.01$, Student's *t*-test with Bonferroni's correction). Using receiver operating characteristic curves, accuracies of 75.6% with *SampEn* and of 87.8% with *MSE* were reached. Our findings show the usefulness of these entropy measures to increase our insight into AD.**

I. Introduction

MAGNETOENCEPHALOGRAPHY (MEG) is a non-invasive technique that allows recording the magnetic fields produced by brain activity. It provides an excellent temporal resolution, orders of magnitude better than other methods for measuring cerebral activity, as magnetic resonance imaging, single-photon-emission computed tomography or positron-emission tomography [1]. A good spatial resolution can also be achieved due to the large number of sensors. Moreover, the activity in different parts of the brain can be monitored simultaneously with whole-head equipments, such as the magnetometer used in the present study [1]. On the other hand, the magnetic signals generated by the human brain are extremely weak. Thus, SQUID (Superconducting QUantum Interference Device) sensors are necessary to detect them. In addition, magnetoencephalograms (MEGs) must be recorded in a magnetically shielded room.

Alzheimer's disease (AD) is the main cause of dementia in western countries [2] and affects approximately 11% of population over 65 years [3]. A definite diagnosis of AD is only possible by necropsy, but a differential diagnosis with other types of dementia and with major depression is used. It includes physical and neurological examination, methods of medical imaging and mental status tests. During the last years, brain recordings analyses have been utilized as a useful tool to complete the diagnosis. Traditionally, AD patients' brain recordings were analyzed with linear techniques. Spectral analysis seems to discriminate AD patients from control subjects through an increased EEG/MEG activity in lower frequency bands associated with AD. Signorino *et al.* [4] found an increase in the EEG powers of delta and theta bands in AD patients compared with control subjects. Other study showed increased slower and reduced faster activity in AD patients' MEGs [5]. Nevertheless, the ability of human brain to perform sophisticated cognitive tasks supports the hypothesis that the brain may not be completely stochastic [6]. Moreover, non-linearity is present in the brain, even at cellular level [7]. Therefore, non-linear analysis of EEG and MEG data might be a complementary tool to help physicians in the AD diagnosis.

The first non-linear methods used to study the brain recordings from AD patients were correlation dimension ($D2$) and the first Lyapunov exponent ($L1$). Jeong *et al.* [8] demonstrated that AD patients exhibit significantly lower $D2$ and $L1$ values than controls in many EEG channels. Other study showed a decreased complexity of the MEG background activity in AD patients in the low frequency bands, and an increased in the high bands [9]. Nevertheless, these classical measures for complexity estimation have some drawbacks. Reliable estimation of $L1$ and $D2$ requires a large number of data points and stationary and noise-free time series [8, 10]. As these problems cannot be solved for physiological signals, other non-linear methods are necessary to study brain recordings. EEG/MEG studies found that AD patients had significantly lower Lempel-Ziv complexity values than elderly control subjects [11, 12]. Using approximate entropy, Abásolo *et al.* [13] found that AD patients' EEGs were more regular than control subjects' recordings. Moreover, Stam *et al.* [14] examined the fluctuation of the EEG synchronization level of AD patients with detrended fluctuation analysis.

In this study, we have examined the MEG background activity in 20 AD patients and 21 control subjects with two non-linear methods: sample entropy (*SampEn*) and

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multiscale entropy (*MSE*). Our purpose was to test the hypothesis that entropy analyses of the magnetic brain activity would be different in both groups, hence indicating an abnormal type of dynamics associated with AD.

II. Materials and Methods

A. Subjects and MEG recording

The signals were acquired with a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) placed in a magnetically shielded room. The subjects lay on a patient bed, in a relaxed state and with their eyes closed. For each subject, MEG registration was performed with a 678.17 Hz sampling frequency, using a hardware band-pass filter of 0.1-200 Hz. Afterward, these recordings were down-sampled by a factor of 4 (169.549 Hz, 50863 samples). Artifact-free epochs of 10 seconds (1696 data points) were selected. Finally, these epochs were filtered between 0.5 and 40 Hz and copied to a computer as ASCII files for further non-linear analysis.

In the present study, MEG signals were recorded from 41 subjects. Cognitive status was screened in both groups with Folstein's Mini Mental State Examination (MMSE). MEGs were obtained from twenty patients (7 men and 13 women; age = 73.05 ± 8.65 years, mean ± standard deviation, SD) fulfilling the criteria of probable AD. They were recruited from the Asociación de Enfermos de Alzheimer (AFAL). Diagnosis for all patients was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA). The MMSE score for these patients was 17.85 ± 3.91 (mean ± SD). Patients were free of other significant medical, neurological and psychiatric diseases than AD and they were not taking drugs which could affect MEG activity.

The control group consisted of 21 elderly control subjects without past or present neurological disorders (9 men and 12 women; age = 70.29 ± 7.07 years, MMSE score = 29.10 ± 1.00 points, mean ± SD). All control subjects and all patients' caregivers signed an informed consent for the participation in this research work. The local Ethics Committee approved this study.

B. Sample entropy (SampEn)

SampEn is an embedding entropy that quantifies the regularity of a signal [15]. *SampEn* is the negative natural logarithm of the conditional probability that two sequences similar for m points remain similar at the next point, where self-matches are not included in calculating the probability [15]. To compute *SampEn*, two input parameters must be specified: a run length m and a tolerance window r. In our study, we have chosen $m = 1$ and $r = 0.25$ times the standard deviation of the original time series, due to these values have been previously used in other AD study [16]. This measure has already been used to study some biological signals. Applied to neonatal heart rate recordings, *SampEn* values fall before clinical signs of sepsis [17]. Kim *et al.* [18] investigated the non-linear characteristics of heart rate variability for different recumbent positions using *SampEn*.

Given a one dimensional time series $X = x(1), x(2),... x(N)$, we describe the algorithm to compute the *SampEn* [15]:

1) Form $N - m + 1$ vectors $X_m(i)$ defined by: $X_m(i) = X_m(i + k)$ with $0 \le k \le m - 1$.
2) The distance between two of this vectors is the maximum difference of their corresponding scalar components:
$$d[X_m(i), X_m(j)] = \max(|x(i+k) - x(j+k)|) \qquad (1)$$
for $0 \le k \le m - 1$.
3) Define $B_i^m(r)$ as $1/(N - m - 1)$ times the number of vectors $X_m(j)$ within r of $X_m(i)$, where $1 \le j \le N - m$ ($j \ne i$). Then, set $B_m(r)$ as:
$$B_m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} B_i^m(r) \qquad (2)$$
4) Similarly, calculate $A_i^m(r)$ as $1/(N - m - 1)$ times the number of j ($1 \le j \le N - m$; $j \ne i$), such the distance between $X_{m+1}(j)$ and $X_{m+1}(i)$ is less than or equal to r. Set $A_m(r)$ as:
$$A_m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} A_i^m(r) \qquad (3)$$
5) Finally, we define:
$$SampEn(m,r) = \lim_{N\to\infty} \left[-\ln \frac{A_m(r)}{B_m(r)} \right] \qquad (4)$$
which is estimated by the statistic
$$SampEn(m,r,N) = -\ln \frac{A_m(r)}{B_m(r)} \qquad (5)$$

C. Multiscale entropy (MSE)

MSE is a non-linear technique to measure complexity over a range of scales [19]. It is based on successive computations of the *SampEn* estimated on coarse-grained time series. *MSE* has been used to analyze cardiac interbeat interval time series from healthy subjects, patients with severe congestive heart failure and subjects with atrial fibrillation [20]. Costa *et al.* [19] found that spontaneous output of the human locomotor system during usual walking is more complex that walking under slow, fast or metronomically-paced protocols. Coding and non-coding DNI sequences have also been analyzed with this complexity measure [21]. In addition, Escudero *et al.* [22] examined the EEG background activity of AD patients and control subjects using *MSE*.

The *MSE* algorithm is as follows [20]. For a time series $X = x(1), x(2),... x(N)$, consecutive coarse-grained time series $Y^\tau = y^\tau(1), y^\tau(2),..., y^\tau(N/\tau)$ should be constructed, according to:
$$y^\tau(j) = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x(i) \qquad 1 \le j \le N/\tau \qquad (6)$$

Afterwards, *SampEn* for each coarse-grained sequence is

calculated.

D. Statistical analysis

Firstly, a statistical analysis was carried out separately for each channel. Student's *t*-tests with the Bonferroni's correction were used to determine if there were any differences between *SampEn* and *MSE* values in both groups.

Secondly, mean values, calculated averaging the results from the 148 channels for each subject, were analyzed with receiver operating characteristic (ROC) curves. This statistical method summarizes the performance of a two-class classifier across the range of possible thresholds. It is a graphical representation of the trade-offs between sensitivity and specificity. Sensitivity is the true positive rate while specificity is equal to the true negative rate:

$$Sensitivity = \frac{TP}{TP + FN} \tag{7}$$

$$Specificity = \frac{TN}{TN + FP} \tag{8}$$

where false negatives (*FN*) are the AD patients classified as control subjects, and false positives (*FP*) are the controls classified as patients. True positives (*TP*) and true negatives (*TN*) are the patients and control subjects correctly recognized, respectively. The area under the ROC curve (AROC) is a single number summary of performance. For a perfect test the area is 1 while an AROC of 0.5 represents a worthless test.

III. Results

SampEn algorithm were applied for the 148 MEG channels with $m = 1$ and $r = 0.25$ times the standard deviation of the original time series. Our results showed that *SampEn* values were higher in the control group than in the AD patients group for all channels. Moreover, the differences were statistically significant in 16 channels ($p < 0.01$, Student's *t*-test with Bonferroni's correction).

We next apply the *MSE* method to the MEG recordings with the same values of *m* and *r*. *MSE* profiles were obtained representing the *SampEn* values of each coarse-grained time series versus the scale factor. These profiles increased on the smaller time scales and then progressively decreased. Fig. 1 shows this performance for the mean values of each group, averaging the *MSE* results of all channels. We estimated the slopes of the profiles for small ($1 \leq$ scale factor ≤ 4) and large time scales ($4 \leq$ scale factor ≤ 8) by means of the least-squares method. For each MEG channel, we compared the slopes of the AD patients group and the control subjects group. In 46 channels, significant differences between both groups were found ($p < 0.01$, Student's *t*-test, Bonferroni's correction) when the slopes for small time scales were analyzed. Moreover, the comparison of the slopes for large time scales revealed significant differences in 99 MEG channels ($p < 0.01$, Student's *t*-test, Bonferroni's correction).

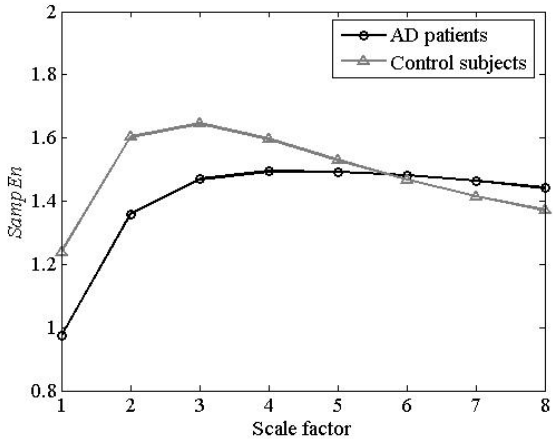

Fig. 1. *MSE* analysis of the 20 AD patients (black curve) and the 21 control subjects (grey curve) with $m = 1$ and $r = 0.25$ times the standard deviation of the original data sequence. The curves were plotted averaging the results of the 148 MEG channels.

Finally, ROC curves were used to assess the ability of our methods to discriminate AD patients from control subjects (Fig. 2). Mean values, obtained averaging the results of all channels, were used in this statistical analysis. With *SampEn* results, sensitivity of 80% and a specificity of 76.2% where achieved at the optimum threshold (1.11). Using the average slopes of the *MSE* profiles for small time scales, we obtained

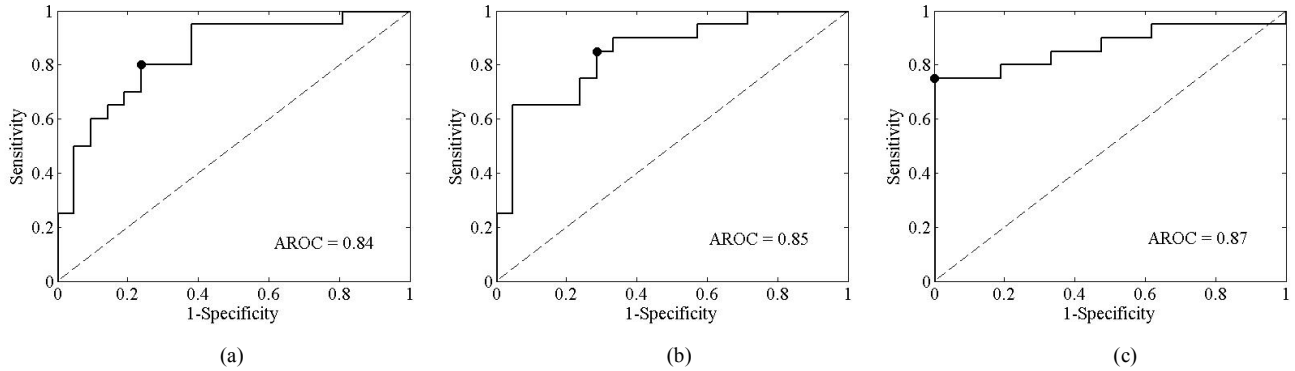

Fig. 2. ROC curves showing the discrimination between AD patients and control subjects with the mean *SampEn* values (a), and with the average slope values of the *MSE* profiles for small (b) and large time scales (c). A solid circle indicates the optimum cut-off point for each ROC curve.

85% sensitivity and 71.4% specificity at an optimum threshold of 0.13. The best results were achieved when the slopes for large scales were analyzed. An accuracy of 87.8% (75% sensitivity, 100% specificity) was reached at a cut-off point of -0.02.

IV. Discussion and conclusions

We have studied the MEG background activity of 20 AD patients and 21 elderly control subjects with *SampEn* and *MSE*. Our purpose was to check the hypothesis that the brain activity recorded in MEG signals was different in AD patients than in control subjects.

Our results revealed that AD patients have lower *SampEn* values at all channels, indicating an increase of the MEG regularity associated with the disease. Our results are in agreement with previous research works that have applied non-linear methods to study the regularity of the brain activity in AD patients [13, 16]. Approximate entropy values were significantly lower in the EEG of AD patients at P3 and P4 [13]. With *SampEn*, statistically significant differences between AD patients and controls were found at parietal and occipital EEG electrodes [16].

The *MSE* analysis showed that AD patients have lower *SampEn* values on the small and medium time scales. If *SampEn* values are higher for one signal than for another at most scale factors, we can assert that the former is more complex than the latter [21]. Thus, our study suggests that brains affected by AD show a less complex physiological behaviour. These results agree with other studies that showed a decreased complexity in the brain recordings of AD patients. For instance, Abásolo *et al.* [11] found significant differences in some EEG channels with Lempel-Ziv complexity. This non-linear complexity measure has also been applied to MEG data [12]. Traditional non-linear methods, $D2$ and $L1$, also have been used to estimate the complexity of EEG/MEG recordings [8, 9].

Some limitations of our study merit consideration. The sample size is small. Thus, a larger database is needed to confirm our results. Moreover, the detected decreased in irregularity and complexity may not be specific to AD and it appears in other pathological states. Finally, our results do not show if *SampEn* and *MSE* can detect a gradation of the disease process.

In conclusion, non-linear analysis of the MEG background activity with *SampEn* and *MSE* revealed an increased regularity and a decreased complexity of the AD patients' recordings. Our results suggest that neuronal dysfunction in AD is associated with differences in the dynamical processes underlying the MEG recording.

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