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# Spectral and Non-linear Analyses of MEG Background Activity in Patients with Alzheimer's Disease

Roberto Hornero*, *Member, IEEE,* Javier Escudero, *Student Member, IEEE*, Alberto Fernández, Jesús Poza, *Student Member, IEEE*, and Carlos Gómez, *Student Member, IEEE*

***Abstract*— The aim of the present study was to analyze the magnetoencephalogram (MEG) background activity from patients with Alzheimer's disease (AD) and elderly control subjects. MEG recordings from 20 AD patients and 21 controls were analyzed by means of two spectral (median frequency and spectral entropy) and two non-linear parameters (approximate entropy and Lempel-Ziv complexity). In the AD diagnosis, the highest accuracy of 75.6% (80% sensitivity, 71.4% specificity) was obtained with the median frequency according to a linear discriminant analysis (LDA) with a leave-one-out cross-validation procedure. Moreover, we wanted to assess whether these spectral and non-linear analyses could provide complementary information to improve the AD diagnosis. After a forward stepwise LDA with a leave-one-out cross-validation procedure, one spectral (median frequency) and one non-linear parameter (approximate entropy) were selected. In this model, an accuracy of 80.5% (80.0% sensitivity, 81.0% specificity) was achieved. We conclude that spectral and non-linear analyses from MEG spontaneous activity could be complementary methods to help in AD detection.**

***Index Terms*— Alzheimer's Disease, approximate entropy, Lempel-Ziv complexity, magnetoencephalogram, median frequency, spectral entropy.**

## I. Introduction

ALZHEIMER'S disease (AD) is a neurodegenerative disorder characterized by the presence of amyloid plaques and neurofibrillary tangles in the brain, accompanied by the loss of cortical neurons and synapses [1]. AD is the most common form of dementia, accounting for 50-60% of all cases. The prevalence of dementia is below 1% in individuals aged 60-64 years, but it shows an almost exponential increase with age. In people aged 85 years or older, the prevalence is between 24% and 33% in the western world [2]. Usually, AD starts by destroying neurons in parts of the brain that are responsible for learning and memory. Then, it affects the brain areas involved in language and reasoning. Finally, individuals may suffer changes in personality and behavior, and even lose their ability to communicate and recognize friends and family members. Although a definite diagnosis is only possible by necropsy, a differential diagnosis with other types of dementia should be attempted. Hence, new approaches are needed to improve AD detection. It is particularly interesting to detect mild cognitive impairment (MCI). This disorder shares several neuropathological and functional characteristics with AD [1]. In this sense, the memory-predominant subtype amnestic MCI is usually considered as a prodromal phase of AD, which is supported by the high conversion rate to AD exhibited by this group of patients [1].

The utility of the electromagnetic brain activity in AD detection [3] has been researched in the last decades from electroencephalogram (EEG) and magnetoencephalogram (MEG) signals. EEG and MEG recordings reflect slightly different characteristics. EEG is sensitive to all primary currents whereas MEG is only affected by currents flows oriented parallel to the scalp [4], [5]. Other difference between EEG and MEG arises from the insensitivity of magnetic fields to inhomogeneities in the head. Electrical activity is more affected than magnetic oscillations by skull and extracerebral brain tissues. Moreover, EEG rhythms can be significantly influenced by some technical and methodological issues, like distance between electrodes, sensor placement or reference point. On the other hand, the magnetic fields emitted by the brain are extremely weak. At the present, MEG signals are detected using large arrays of SQUIDs (superconducting quantum interference devices) immersed in a cryogen, which should be housed in a thermally insulated container. In addition, the MEG instrumentation should be placed in a magnetically shielded room to reduce the environmental noise. This issue increases the cost of the system and reduces both

Manuscript received July 18, 2007. This work was supported in part by the "Consejería de Educación de la Junta de Castilla y León" under project VA108A06. *Asterisk indicates corresponding author.*

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the mobility and the availability of this kind of recording [5]. In sum, we center our study in MEG signals because this recording is less distorted by head structures and provides reference-free recordings [5].

Several works have focused on a spectral analysis from spontaneous MEG activity in AD patients. A slowing of MEG rhythms in AD has been observed using both relative power values and several spectral indexes like mean frequency, peak frequency and transition frequency [6], [7]. MEG studies using spectral entropy also reported a decrease in irregularity of AD patients' MEG activity when compared with that of healthy controls' [7]. Both a decrease of coherence values in the alpha band [8] and a general decrease of coherence in all frequency bands [9] have been observed in AD patients' MEG recordings.

From another point of view, non-linear methods can be useful to analyze electromagnetic brain signals [3], [10]. Non-linearity in the brain is introduced even at the neuronal level [11]. Thus, EEG and MEG appear to be an appropriate area for non-linear analysis, which can complement the information about the brain activity provided by a spectral analysis [3], [10], [12]. Several studies have examined the AD patients' EEG/MEG recordings with non-linear analysis methods. The first non-linear methods applied to electromagnetic brain signals were the correlation dimension ($D2$) and the first Lyapunov exponent ($L1$) [12], [13]. Several studies have found that AD may produce lower $D2$ and $L1$ values [3], [13]. Nevertheless, there are some major drawbacks in the application of both $D2$ and $L1$ to EEG or MEG. Reliable estimation of $D2$ and $L1$ requires a large quantity of data, stationary and noise free time series [14]. These assumptions cannot be achieved for physiological data. Thus, it becomes necessary to apply other non-linear analyses in order to properly study these recordings. For example, a suitable fractal dimension measure has been recently applied to classify EEG recordings from AD patients [15]. Other methods like approximate entropy (*ApEn*) or sample entropy have showed a decreased irregularity with AD [16], [17]. In addition, Lempel-Ziv complexity (*LZC*) provided lower values in AD patients' MEG [18]. Moreover, AD has also been studied applying connectivity measures such as mutual information and synchronization likelihood to EEG/MEG data [19]-[21].

The aim of the present study was to analyze the AD patients and controls' MEG background activity by means of two spectral (median frequency and spectral entropy) and two non-linear parameters (*ApEn* and *LZC*). These features were compared to verify which obtained the highest accuracy in the classification of AD patients from MEG signals. Moreover, we wanted to assess whether these spectral and non-linear parameters could provide complementary information to improve the AD diagnosis.

## II. Subjects and Magnetoencephalogram Recordings

Twenty AD patients and 21 elderly control subjects participated in this study, which was approved by the local ethics committee. Informed consent was obtained from all control subjects and AD patients' caregivers.

The AD patients (9 men and 11 women; age = 73.10 ± 9.71 years, mean ± standard deviation, SD) were recruited from the "Asociación de Familiares de Enfermos de Alzheimer" in Spain. They fulfilled the criteria of probable AD according to the guidelines provided by the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [22]. To diagnose this dementia, brain scans (SPECT and MRI) and thorough medical, physical, neurological, psychiatric, and neurophysiological examinations were performed. Mini-Mental State Examination (MMSE) and Functional Assessment Staging (FAST) scores in this group were 17.70 ± 3.89 and 4.05 ± 0.39 (mean ± SD), respectively. No patient was receiving medication that could affect the MEG activity.

Eight men and 13 women without past or present neurological disorders formed the control group. Their average age was 70.19 ± 6.96 years (mean ± SD). The MMSE and FAST scores for this group were 29.05 ± 0.97 and 1.71 ± 0.46 (mean ± SD), respectively. The difference in age between both groups was not significant ($p$-value = 0.2752, Student's $t$-test).

MEGs were recorded using a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) placed in a magnetically shielded room at the "Centro de Magnetoencefalografía Dr. Pérez-Modrego", Spain. In order to reduce artifactual contamination, the MEGs were recorded while the subjects lay comfortably on a patient bed in a relaxed state, awake and with eyes closed. From each subject, five minutes of MEG background activity were acquired at a sampling rate of 678.19 Hz. To reduce the data length, MEGs were downsampled to 169.549 Hz. Afterward, they were digitally filtered between 1.5 Hz and 40 Hz in order to reduce ocular and muscle activity. An average number of 18.44 ± 7.30 (mean ± SD) artifact-free MEG epochs of 10 s (1695 samples) were selected for further analysis at each sensor for each subject. It should be noticed that the selection of artifact-free segments was based upon visual inspection by an experienced physician assisted with an amplitude thresholding method, who was blind to the subjects' diagnosis.

## III. Methods

MEG epochs were analyzed by means of two spectral (median frequency and spectral entropy) and two non-linear parameters (*ApEn* and *LZC*).

### A. Median frequency (MF)

Mean frequency and *MF* have been used to measure the changes produced by different mental disorders in EEG or MEG activity [3], [7], [23], [24], since they are simple indices that summarize the whole spectral content of the power spectral density (*PSD*).

Before calculating *MF*, the MEG power spectra were estimated. First of all, the autocorrelation function of each MEG epoch was computed. The *PSD* was obtained as the Fourier transform of the autocorrelation vector, thus being the spectral resolution of this study equal to 0.05 Hz. Then, MEG recordings were analyzed using the *MF*, which is defined as the frequency that contains 50% of the *PSD* power. Considering the 1.5 Hz – 40 Hz frequency band used in this study, the *MF* was estimated from:

$$\frac{1}{2}\left[\sum_{f=1.5\text{Hz}}^{40\text{Hz}} PSD(f)\right] = \sum_{f=1.5\text{Hz}}^{MF} PSD(f). \quad (1)$$

### B. Spectral entropy (SpecEn)

*SpecEn* was computed in order to quantify the flatness of the spectrum [25]. *SpecEn* characterizes the distribution of *PSD* by assessing the disorder of the spectrum. Several studies have already applied *SpecEn* to analyze of EEG/MEG signals [25]-[28], including AD patients' recordings [7], [17]. To estimate this parameter, the *PSD* was normalized ($PSD_n$) so that $\sum PSD_n(f) = 1$. Then, the Shannon's entropy was applied to the $PSD_n$ [26]:

$$SpecEn = \frac{-1}{\log(M)} \sum_{f=1.5\text{Hz}}^{40\text{Hz}} PSD_n(f)\log[PSD_n(f)], \quad (2)$$

where *M* is the number of frequency bins and the division by log(*M*) normalizes the *SpecEn* to a scale from 0 to 1 [25].

*SpecEn* can be used as an irregularity estimator [26]. High *SpecEn* values imply a broad and flat spectrum (e.g., white noise), whereas a predictable signal whose frequencies are mainly condensed into few frequency bins (e.g., a sum of sinusoids) provides a low *SpecEn* value [25].

### C. Approximate Entropy (ApEn)

*ApEn* is a family of statistics that quantifies the signal regularity, notwithstanding its stochastic or deterministic origin [29], [30]. It assigns higher values to more random data [29]. *ApEn* can be applied to short and relatively noisy time series and it is insensitive to infrequent artifacts or outliers, even those of large magnitude [30]. Thus, this statistic has been widely used to extract potentially useful information from biomedical time series [16], [27], [28], [30], [31].

Although *ApEn* was constructed along similar lines to the Kolmogorov-Sinai entropy, it was developed to provide a model-independent, widely applicable formula that could distinguish relatively short, noisy signals by their regularity [28], [30]. Consequently, *ApEn* avoids the problems derived from the application of *KS* entropy to biomedical data sets [29].

*ApEn* can be interpreted as a statistic which assesses the average of the logarithm of a conditional probability. On the other hand, it is an entropic measure which estimates the rate of new pattern generation [31]. Recent studies have shown that this variable depends on both the spectra and the probability density function of the time series [28], and increases with frequency and bandwidth [31].

*ApEn* has two input parameters: a run length *m* and a tolerance window *r*. It measures the logarithmic probability that runs of patterns that are close (within *r*) for *m* contiguous observations remain close (within the same *r*) on subsequent incremental comparisons [29], [30]. The detailed algorithm for the computation of *ApEn* from a time series, $\{x(i)\} = x(1), x(2), \ldots, x(N)$, of length *N* is as follows [29], [31]:

1. Form $N-m+1$ vectors $X(1), \ldots, X(N-m+1)$ defined by: $X(i) = [x(i), \ldots, x(i+m-1)]$, with $1 \le i \le N-m+1$.
2. Define the distance between $X(i)$ and $X(j)$, $d[X(i),X(j)]$, as the maximum absolute difference between their respective scalar components:
$$d[X(i), X(j)] = \max_{k=1,\ldots,m} |x(i+k-1) - x(j+k-1)|. \quad (3)$$
3. For a given $X(i)$, count the number of $j$ ($j = 1, \ldots, N-m+1$, $j \neq i$) so that $d[X(i), X(j)] \le r$, denoted as $N^m(i)$. Then, for $1 \le i \le N-m+1$:
$$C_r^m(i) = N^m(i)/(N-m+1). \quad (4)$$
4. Compute the natural logarithm of each $C_r^m(i)$, and average it over $i$,
$$\phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln C_r^m(i). \quad (5)$$
5. Increase the dimension to $m+1$ and repeat steps 1) to 4) to find $C_r^{m+1}(i)$ and $\phi^{m+1}(r)$.
6. *ApEn* is estimated as [29]:
$$ApEn(m, r, N) = \phi^m(r) - \phi^{m+1}(r). \quad (6)$$

Both *m* and *r* are critical in the performance of *ApEn*. However, there are no guidelines for optimizing their values. Since *ApEn* is nearly unaffected by noise of magnitude below *r* [30], the value of this parameter should be larger than most of the noise [29]. In addition, for small *r* values, poor conditional probability estimations may be obtained. On the other hand, the accuracy and confidence of the *ApEn* estimation improve as the number of matches of length *m* and $m+1$ increases. This can be achieved by choosing small *m* and large *r*. However, some problems may arise when the matching criterion is too relaxed and too large *r* values may provoke the loss of system information [29].

In this study, *ApEn* was computed with the established parameters of $m = 1$ and $r = 0.25$ times the SD of the analyzed signal [29]. The parameter *r* was normalized to give *ApEn* a translation and scale invariance. These parameters provide good statistical reproducibility for sequences longer than 60 samples, as considered herein [29], [30].

### *D. Lempel-Ziv complexity (LZC)*

*LZC* is a model-independent measure which evaluates the complexity in the Kolmogorov's sense, also referred as algorithmic complexity [18], of a time series (i.e., the complexity of a sequence is given by the number of bits of the shortest computer program which can generate it) [32]. It is related to the number of distinct substrings and their recurrence rate along the signal. *LZC* provides higher values to more complex data [32]. This metric has been applied in many different areas, including the analysis of biomedical signals [33]. For instance, it was applied to EEG and MEG signals from AD patients [18], [34] or to assess the depth of sedation [27], [28]. Although the evaluation of a complexity measure in this sense seems general and computer-dependent, the *LZC* is able to avoid these problems [32], [35]. The reason is that its calculation needs only two simple operations: sequence comparison and number accumulation [32].

*LZC* also contains a notion of complexity in a statistical sense, since it is related to the Shannon's entropy, characterizing the average information quantity in a signal [35]. Several studies have shown that *LZC* mainly depends on the signal bandwidth, although a slight dependence on the sequence probability density function was also found [28], [33]. Additionally, *LZC* could be interpreted as a harmonic variability metric [33]. Therefore, this statistic may be closely related to linear properties of the data.

Due to the fact that *LZC* analyzes a finite symbol sequence, $P = s(1), \ldots, s(N)$, the given signal must first be coarse-grained [27]. In this study, a binary (zeros and ones) conversion was used, since previous studies found that this kind of conversion may keep enough signal information [27], [33]. To compute $P$, the following criterion was applied [27], [33]:

$$s(i) = \begin{cases} 0 & if\ x(i) < T_d \\ 1 & if\ x(i) \geq T_d \end{cases} \tag{7}$$

where $T_d$ denotes the threshold used in the coarse-grained conversion. In this study, $T_d$ was fixed to the median of the analyzed signal, since partitioning about the median is robust to outliers [36].

The string $P$ is scanned from left to right and a complexity counter $c(N)$ is increased by one unit every time a new subsequence of consecutive symbols is found in the scanning process. An example of this procedure can be found in [27]. Afterward, $c(N)$ is normalized to obtain a complexity measure independent of the sequence length. If the number of different symbols is $\alpha$, the upper bound of $c(N)$ is given by [32]:

$$c(N) < N/\left[(1-\varepsilon_N)\log_\alpha(N)\right] \tag{8}$$

where $\varepsilon_N$ is a small quantity and $\varepsilon_N \to 0$ ($N \to \infty$). In general, $N/\log_\alpha(N)$ is the upper limit of $c(N)$:

$$\lim_{N\to\infty} c(N) = b(N) \equiv N/\log_\alpha(N). \tag{9}$$

For a binary conversion $\alpha = 2$, $b(N) \equiv N/\log_2(N)$, and $c(N)$ can be normalized via $b(N)$:

$$C(N) = c(N)/b(N). \tag{10}$$

The normalized *LZC* reflects the arising rate of new patterns along with the sequence [27]. A minimum data length must be considered to ensure that the *LZC* reveals real data features. A previous study carried out on a similar database showed that the *LZC* values become stable for MEG signals longer than 1000 or 1500 samples [18]. Thus, an epoch length of 1695 data points (10 seconds) was used in this study.

### *E. Statistical analysis*

Both the Kolmogorov–Smirnov and the Shapiro–Wilk tests were used to assess normality of distribution, whereas homocedasticity was verified with Levene's test. After the exploratory analysis, variables met parametric test assumptions. Therefore, a one-way analysis of variance (ANOVA) with age as a covariate was applied to assess statistical significance ($\alpha$ = 0.01). The distribution of each parameter was represented using notched boxplots, and receiver operating characteristics (ROC) curves were used to visually evaluate the ability of each parameter to distinguish between both groups.

A linear discriminant analysis (LDA) and a forward stepwise LDA with a leave-one-out cross-validation scheme were performed to investigate group classification. Results were showed in terms of sensitivity (i.e., proportion of all AD patients for whom there is a positive test), specificity (i.e., percentage of healthy subjects properly identified) and accuracy (i.e., total fraction of subjects well classified).

## IV. RESULTS

### *A. Evaluation of MF, SpecEn, ApEn, and LZC*

In order to perform the spectral analyses, a mean PSD per subject and channel was obtained from the 10 s epochs in the 148 MEG channels. These PSD functions were characterized with their *MF* and *SpecEn*. *ApEn* and *LZC* were calculated for each MEG epoch, and the corresponding values were averaged for every MEG channel and subject. Therefore, we obtained a set of 148 values per subject and parameter. Due to the high spatial density of the MEG channels, the problem dimensionality was reduced by computing the mean of the 148 values for each subject and parameter in order to simplify further analyses. Thus, the statistical analyses were performed using only one mean value of *MF*, *SpecEn*, *ApEn*, and *LZC* per subject.

Graphical summaries of the distributions from each parameter are depicted in Fig. 1, which shows the corresponding notched boxplots. The average *MF* value for the control group was 13.06 ± 2.95 Hz (mean ± SD), whereas it reached 9.18 ± 2.13 Hz for the AD patients. Control subjects had also higher entropy values than AD patients. Average

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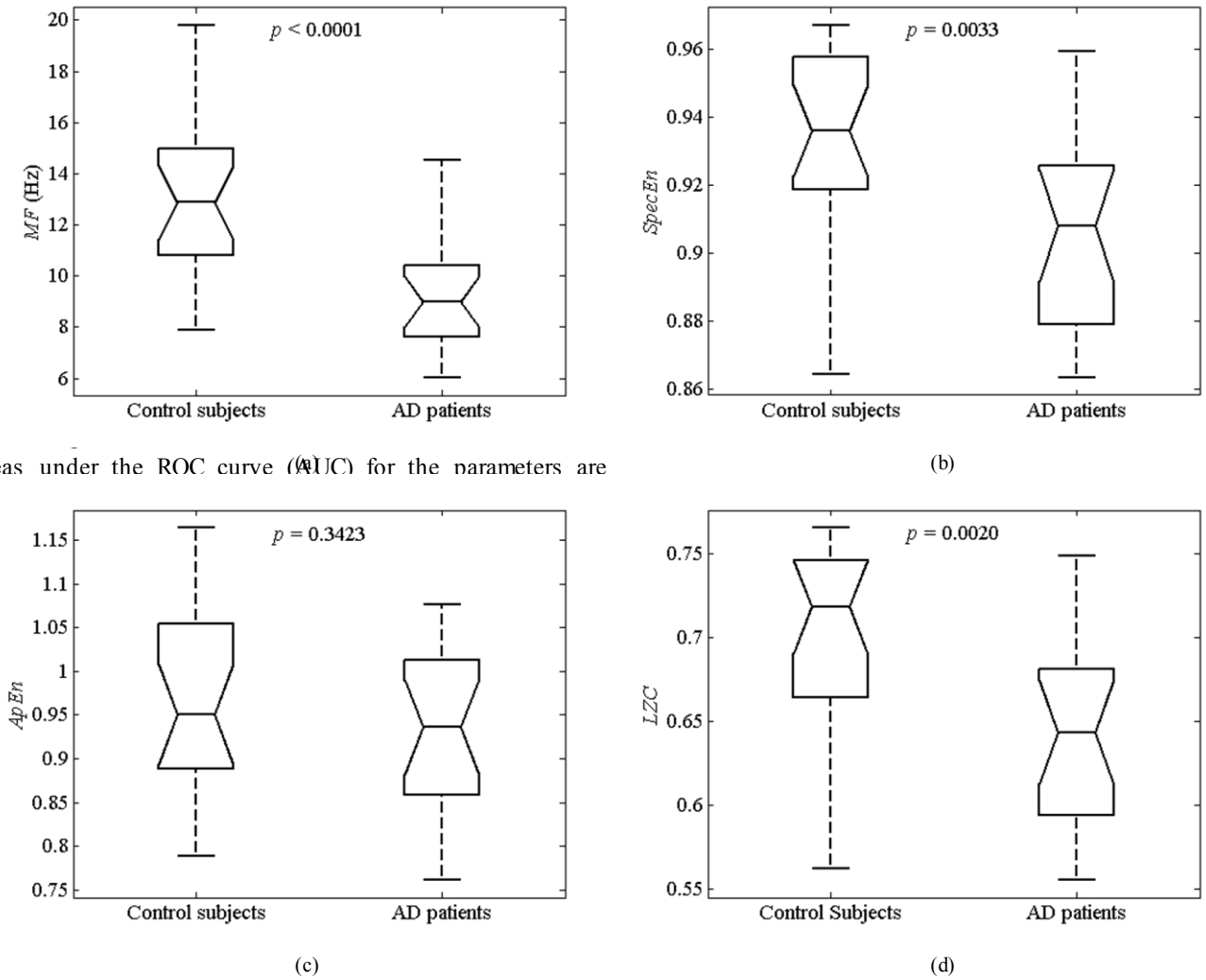


Fig. 1. Notched boxplots showing the distribution of each variable averaged across all MEG channels for both groups and the corresponding *p*-values with age as a covariate. (a) Median frequency (*MF*). (b) Spectral entropy (*SpecEn*). (c) Approximate entropy (*ApEn*). (d) Lempel-Ziv complexity (*LZC*)

TABLE I
AUC, SENSITIVITY, SPECIFICITY, AND ACCURACY OBTAINED FOR EACH PARAMETER AND FOR A FORWARD STEPWISE LDA. A LEAVE-ONE-OUT CROSS-VALIDATION PROCEDURE WAS USED.

| | AUC | Sensitivity (%) | Specificity (%) | Accuracy (%) |
|---|---|---|---|---|
| *MF* | 0.8571 | 80.0 | 71.4 | 75.6 |
| *SpecEn* | 0.7809 | 70.0 | 76.2 | 73.2 |
| *ApEn* | 0.6143 | 50.0 | 52.4 | 51.2 |
| *LZC* | 0.7833 | 65.0 | 76.2 | 70.7 |
| LDA: *MF* and *ApEn* | 0.8857 | 80.0 | 81.0 | 80.5 |

AUC: area under the ROC curve; LDA: linear discriminat analysis; *MF*: median frequency; *SpecEn*: spectral entropy; *ApEn*: approximate entropy; *LZC*: Lempel-Ziv complexity.

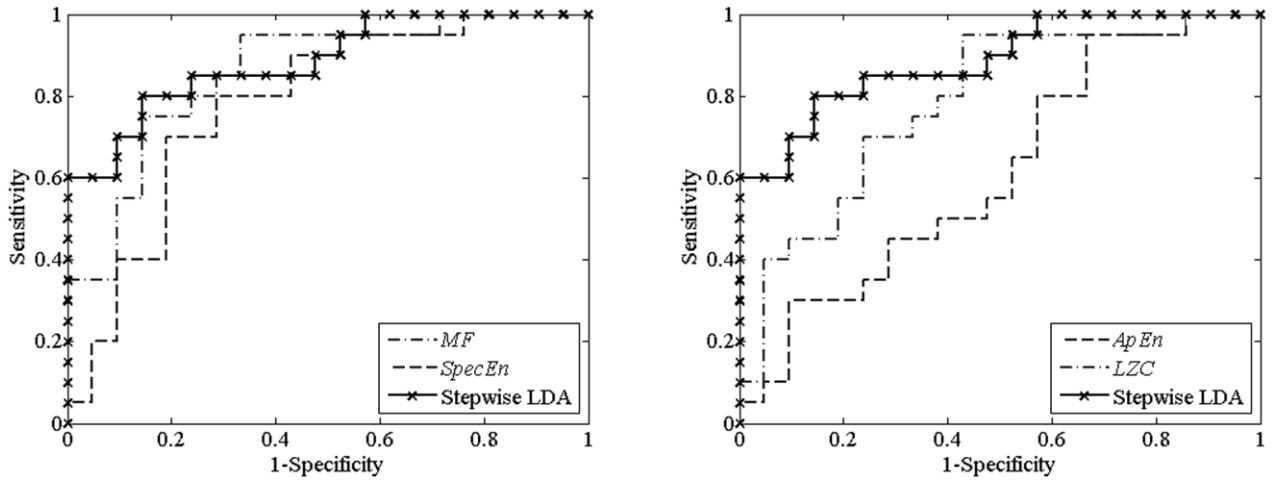


Fig. 2. ROC curves for each parameter and for the model obtained with a forward stepwise LDA, which included *MF* and *ApEn*. (a) Spectral parameters (*MF* and *SpecEn*) and the LDA model. (b) Non-linear parameters (*ApEn* and *LZC*) and the LDA model.

After a forward stepwise LDA with a leave-one-out cross-validation procedure, one spectral parameter (*MF*) and one non-linear parameter (*ApEn*) were automatically selected. The first variable to enter the model was *MF*, since it provided the best classification between AD patients and control subjects. At the next step, *ApEn* was added to the model used by the stepwise LDA to classify the subjects. The reason was that *ApEn* provided a greater discriminatory ability than *SpecEn* and *LZC* when used in conjunction with *MF*. Finally, at the last step, *SpecEn* and *LZC* were left out of the analysis, since they were linearly related to the parameters that had already been included into the model and provided no additional information. It is noteworthy that the discriminant model based on *MF* and *ApEn* outperformed the standard LDA with single parameters. In this sense, an accuracy of 80.5% (80.0% sensitivity, 81.0% specificity) was achieved by applying the classification function to the data set. This fact implies an increase of 4.9% in the accuracy with respect to the result obtained using only *MF*. Furthermore, the AUC achieved by combining *MF* and *ApEn* was higher than those obtained for each single parameter.

## V. Discussion and Conclusions

We analyzed the MEG recordings from 20 AD patients and 21 elderly control subjects by means of two spectral (*MF* and *SpecEn*) and two non-linear parameters (*ApEn* and *LZC*). Our results showed diminished *MF* values with significant differences in AD patients' MEG. These findings are in agreement with previous studies, which also confirmed the slowing of spontaneous MEG or EEG activity in AD patients [3], [6]. The *MF* parameter reached the highest accuracy of 75.6% (80.0% sensitivity, 71.4% specificity) with a leave-one-out cross-validation procedure when comparing controls and AD patients' MEG.

*SpecEn* and *ApEn* values were lower in AD patients' MEG. These parameters can be used as irregularity estimators [26], [29]. Thus, we can state that controls' MEG background activity is more irregular than that of AD patients. These results confirm other studies where a lower irregularity in AD patients' MEG or EEG was found [7], [17]. Regarding to *LZC* values, these were lower in AD patients' MEG, indicating an abnormal MEG background activity in AD patients. These results also confirmed other research works that applied complexity measures to EEG/MEG recordings of AD patients [3], [13], [18].

Spectral parameters have shown a slowing of spontaneous MEG activity in AD. In this sense, some authors have pointed out that the cholinergic system modulates the spontaneous cortical activity at the theta and alpha bands, along with the functional coupling in the theta band [37]. Given that cholinergic deficit involves a loss of the neurotransmitter aceltylcholine, this fact can be partly responsible of MEG slowing in AD patients. Additionally, non-linear parameter results suggest that MEG activity from AD patients is characterized by a lower degree of irregularity and complexity. These facts could be explained by a decrease of dynamical complexity in some parts of the brain. However, the pathophysiological implications of these alterations are not clear. Among others, three mechanisms can be responsible for it: neuronal death, a general effect of neurotransmitter deficiency and connectivity loss of local neural networks due to nerve cell death [3]. Nevertheless, ageing and age-related diseases often accompany a wide-ranging loss of physiological complexity [38].

To improve the AD diagnosis, we wanted to assess whether these spectral and non-linear analyses could provide complementary information. We applied a forward stepwise LDA with a leave-one-out cross-validation procedure, which automatically selected a spectral parameter (*MF*) and a non-linear parameter (*ApEn*). On the other hand, *SpecEn* and *LZC*

did not enter the model, since they were linearly related to the parameters already included into the model and they did not improve the subject classification based on both *MF* and *ApEn*. Table I shows that the highest accuracy of 80.5% was obtained with this procedure (80.0% sensitivity, 81.0% specificity). This result implies that the combination of *MF* and *ApEn* may provide a more reliable model to detect AD than that obtained using single parameters. In this sense, it is noteworthy that the combined metric correctly detected some subjects that were misclassified by one or more single parameters, which is due to the fact that spectral and non-linear measures can yield complementary information [3], [10], [12], useful to characterize AD. Furthermore, this compares well with other studies, reported by the American Academy of Neurology, which provide a sensitivity of 81% and specificity of 70% [39].

Some limitations of our study merit consideration. The sample size was small. As a result, our findings are preliminary. Hence, to prove the usefulness of our proposed method with *MF* and *ApEn* as a diagnostic tool, this approach should be extended to a much larger patient population. Moreover, the detected decrease of irregularity and complexity in the electromagnetic brain activity is not specific to AD. It appears in several physiological and pathological states including, among others, anesthesia [27] or vascular dementia [13]. In a similar sense, both EEG and MEG slowing have also been reported in other neurodegenerative diseases [24] and it can be particularly interesting to distinguish MCI patients from control subjects in order to predict AD [23]. Finally, it should be mentioned that the results from each parameter were averaged to simplify the analyses. This issue involves a loss of spatial information, which could be partially avoided by computing the mean of each parameter for a number of brain regions. However, in that case, it should be taken into account that a recording channel does not necessarily measure only the brain rhythms under that sensor, but it can reflect activity from other areas.

In summary, we conclude that spectral and non-linear analyses could provide complement information to improve the AD diagnosis from MEG background activity. We achieved an accuracy of 80.5% (80.0% sensitivity, 81.0% specificity) after a forward stepwise LDA with a leave-one-out cross-validation procedure. In this model, a spectral parameter (*MF*) and a non-linear parameter (*ApEn*) were selected. However, further work is now required to test the potential value of our methodology at each brain region with a larger data set and with other types of dementia.

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TABLE II

Average $ApEn(M,R)$ values



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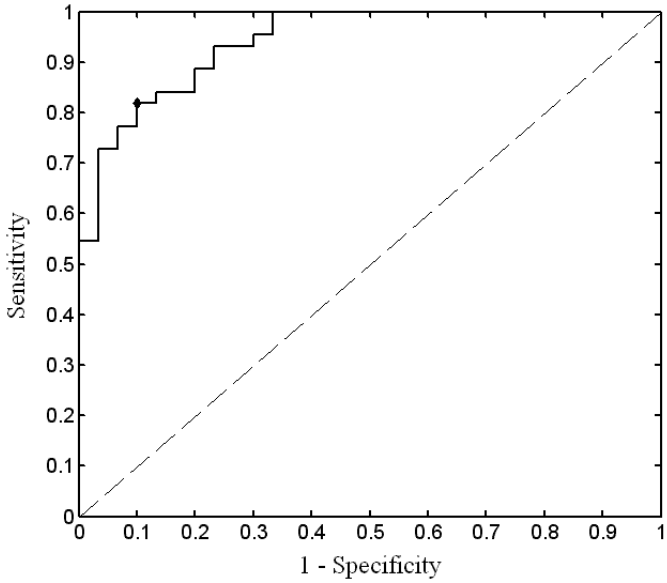


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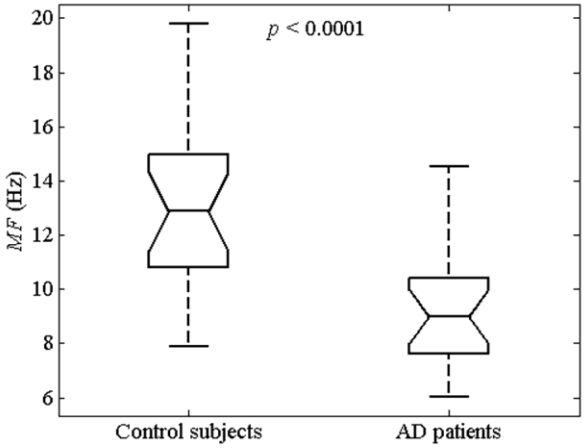


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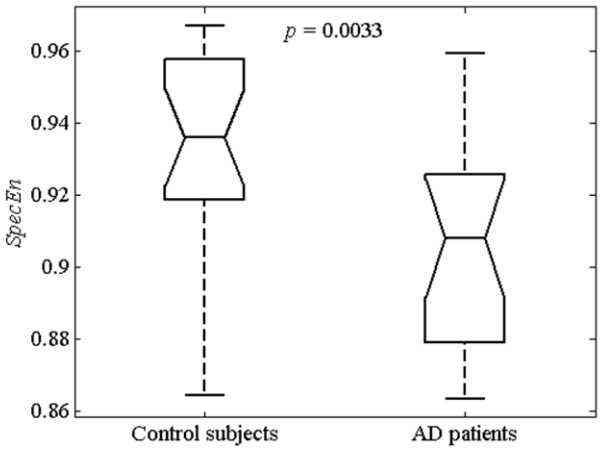


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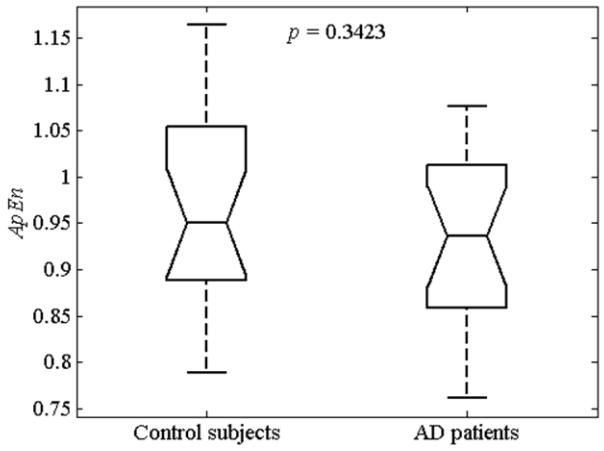


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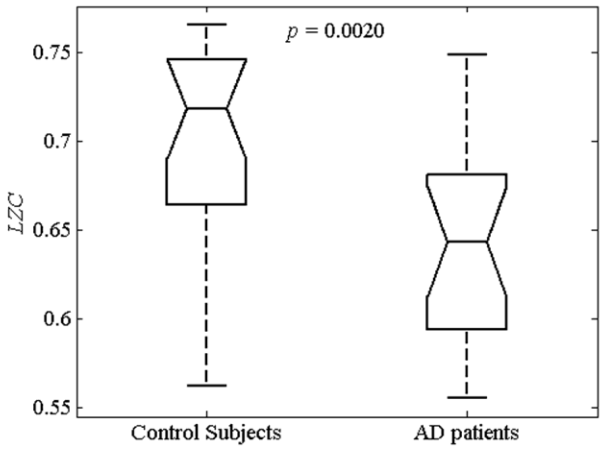


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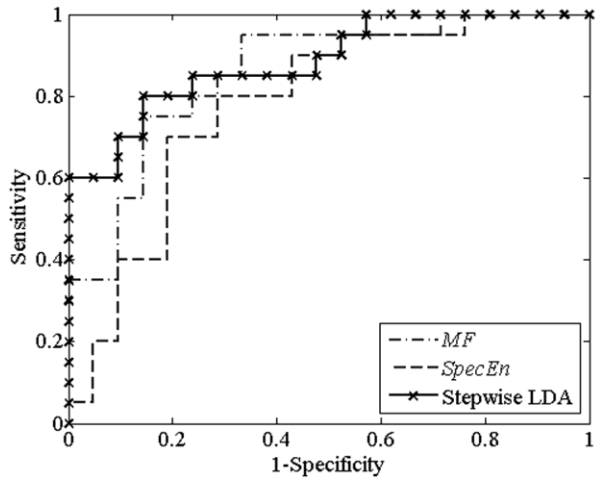


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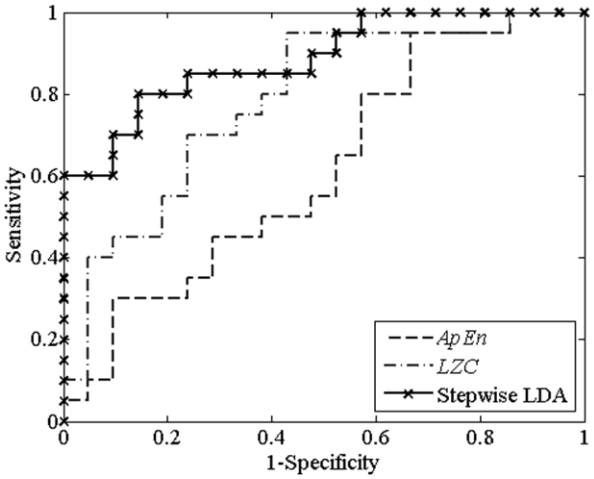


Fig. 2b.