Spectral and Non-Linear Analyses of Spontaneous Magnetoencephalographic Activity in Alzheimer's Disease

Jesús Poza, PhD*; Carlos Gómez, PhD; Alejandro Bachiller, MS; and
Roberto Hornero, PhD

Biomedical Engineering Group, Department "Teoría de la Señal y Comunicaciones e Ingeniería Telemática", E.T.S. Ingenieros de Telecomunicación, University of Valladolid, Paseo de Belén, 15, 47011 - Valladolid, Spain

Submitted April 2011. Accepted for publication December 2011.

ABSTRACT

Alzheimer's Disease (AD) is considered the most prevalent form of dementia. A definite AD diagnosis is established after examination of brain tissue. However, an accurate identification should be attempted to effectively apply therapeutic strategies. The aim of the present study was to perform regional analysis of spontaneous magnetoencephalographic (MEG) activity to describe brain dynamics in AD. Several spectral and non-linear parameters were calculated to obtain a comprehensive description of the spatial abnormalities in brain dynamics. Our findings showed a significant global slowing of MEG activity in AD, as well as a significant loss of irregularity and complexity in several brain regions. Spectral and non-linear parameters reached classification accuracies of around 80%. The results suggest the potential usefulness of spectral and non-linear parameters to characterize the cognitive and functional abnormalities of dementia. These parameters can yield information useful in clinical AD diagnosis and provide further insights on underlying brain dynamics.

Keywords: Alzheimer's disease, magnetoencephalogram, non-linear analysis, spectral analysis

1. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative pathology characterized by deterioration in cognition and memory, progressive impairment in the ability to carry out activities of the daily living, as well as a number of behavioural and psychological symptoms [1]. AD accounts for about 60% of all dementia cases in developed and

*Corresponding author: Jesús Poza, Biomedical Engineering Group, Department T.S.C.I.T., E.T.S. Ingenieros de Telecomunicación, University of Valladolid, Paseo de Belén, 15, 47011 – Valladolid, Spain. Phone: +34 983 423000 (5569). Fax: +34 983 423667. E-mail: jespоз@tel.uva.es. Other authors: cargom@tel.uva.es; bachillermatarranz@gmail.com; robhor@tel.uva.es.

developing countries [2, 3], and represents the leading form of age-related dementias. Several risk factors have been identified, with ageing being the most important one [2]. The relevance of ageing is derived from the increase in life expectancy of the world population, which contributes to the AD prevalence [2, 3].

Clinical diagnosis of AD is usually based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke - AD and Related Disorders Association (NINCDS-ADRDA) [4]. The NINCDS-ADRDA guidelines establish AD diagnosis by means of a complete medical history, as well as physical, psychiatric and neurological examinations [5]. Additionally, laboratory studies, such as thyroid-function tests and assessment of vitamin B12 deficiency, are recommended to identify other forms of dementia and coexisting disorders associated with ageing. Structural neuroimaging techniques such as computer tomography (CT) or magnetic resonance imaging (MRI) are also appropriate to exclude other causes of dementia [5].

Despite the aforementioned test batteries, there are no definitive imaging or laboratory tests to detect AD. Thus, NINCDS-ADRDA criteria establish several categories depending on the confidence in the diagnosis: unlikely, possible and probable. A definite diagnosis can only be made by post-mortem examination of brain tissue [5, 6]. Regardless of the difficulties in diagnosis, an accurate and early identification of AD is crucial to significantly alleviate the most devastating symptoms [7], due to the fact that an optimal treatment requires both nonpharmacological and pharmacological interventions in early stages [1]. Advances in diagnosis, treatment and disease management are highly important in coping with AD.

The analysis of electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings is one of the promising tools to help in AD diagnosis. EEG and MEG signals can reflect anatomical and functional deficits of the brain cortex damaged by AD at an early stage of the disease [8]. Accumulated evidence suggests that the analysis of electromagnetic brain activity during mental rest provides significant insights on the ageing processes and cognitive decline from neurodegeneration [9]. Although both EEG and MEG rhythms are generated by synchronous oscillations of pyramidal neurons, they reflect slightly different characteristics of the electromagnetic brain activity. EEG signals measure the electric fields induced by all primary currents, whereas MEG recordings are sensitive only to current flows oriented parallel to the scalp [10]. Scalp EEG is strongly influenced by several technical and methodological issues and some authors suggested that scalp EEG can be viewed as the result of a spatial filtering of the electrocorticogram by the volume conductor [11]. Therefore, MEG might provide a more accurate vision of the ongoing brain activity than scalp EEG [10, 11].

Since 1980s, EEG activity has been widely analyzed to obtain pathological patterns associated with AD [9, 12, 13]. On the contrary, analysis of MEG patterns associated with AD is a relatively recent research field [13, 14]. The abnormalities that AD produces in spontaneous MEG oscillations were initially analyzed using conventional signal processing methods, such as spectral analysis. Hence, an increase in the relative power of slow frequency bands together with a reduction in the relative power of high frequency bands have been reported in several MEG studies on AD

[15–21]. The slowing of MEG activity in AD has also been observed by means of spectral quantifiers such as mean frequency [17, 22], individual alpha peak [16, 22, 23], transition frequency [22] and several spectral ratios [20]. On the other hand, several studies have addressed the characterization of non-linear dynamics associated with AD [14]. The fundamental assumption of these studies is that MEG signals are generated by non-linear deterministic processes with non-linear coupling interactions between neuronal populations. Based on the previous idea, a loss of complexity has been described in AD patients' spontaneous MEG activity by means of several non-linear parameters, such as correlation dimension [24], Lempel-Ziv complexity [25–29], Higuchi's fractal dimension [29, 30] and multiscale entropy [27], although some works have suggested that the loss of complexity could be only found in high frequency bands [31]. Entropy-related statistics have shown that this decrease in complexity is accompanied by a regularity increase. Thus, a global regularity increase has been found using spectral entropies, such as Shannon, Tsallis and Rényi entropies [22, 32, 33]. Non-linear measures, like approximate entropy [29, 32], sample entropy [26, 27, 29] and auto-mutual information [27, 34], support the global loss of irregularity. On the other hand, studies analyzing functional connectivity have identified a decrease of coherence in the alpha [35, 36], beta and gamma bands [35], as well as a general loss of coherence in all frequency bands [15]. Altered temporal correlations [37] and reduced level of synchronization in specific frequency bands [13, 38–40] have also been reported, which suggest a loss of functional connectivity. Likewise, it has been shown that AD is characterized by specific changes of long and short distance interactions in several frequency bands [39, 41]. Finally, it is noteworthy that the aforementioned methods can provide complementary information. Thus, an MEG study suggested that the combination of spectral parameters could be useful to improve the classification accuracy in AD detection [22]. Similarly, the combination of spectral and nonlinear parameters has been successfully employed to increase the classification performance of AD patients and controls [32].

The aim of the present study is to perform regional analysis of MEG activity to describe brain dynamics in AD. We analyzed the spontaneous MEG activity in 36 patients with probable AD and 26 elderly control subjects, using several spectral and non-linear parameters. These methods have shown their ability to characterize the abnormalities associated with AD patients' MEG activity, such as the slowing of the power spectrum, the loss of irregularity from a spectral and a non-linear point of view, and the decrease in complexity. Furthermore, we analyzed and discussed the potential usefulness of these parameters to help in the complex AD diagnosis.

2. MATERIALS

2.1. Subjects

Thirty-six patients (12 men and 24 women, age = 74 ± 7 yr, mean $\pm$ standard deviation [SD]) from the “Asociación de Familiares de Enfermos de Alzheimer” of Madrid and twenty-six cognitively normal volunteers (9 men and 17 women, age 72 ± 6 years, mean $\pm$ SD) participated in the study. The patients included in the study were men and women

> 60 years of age with a diagnosis of probable AD (mild to moderate) according to the guidelines of the NINCDS-ADRDA [4]. They were pseudo-randomly selected and were collaborative in the MEG recording procedure. AD patients were excluded for the following reasons: atypical evolution according to NINCDS-ADRDA criteria (sudden onset, focal neurological findings and convulsions or abnormalities in the first stages of disease evolution); no Mini-Mental State Examination (MMSE) or Global Deterioration Scale/Functional Assessment Staging (GDS/FAST) score; clinical history of stroke, primary psychotic disorder or of any disease that would by itself explain the clinical syndrome; dementia due to multiple aetiologies; history of alcohol or substance abuse; or metal braces or pacemaker that may interfere with the MEG equipment. Their cognitive function was evaluated using the MMSE, whereas functional status was evaluated by means of the GDS/FAST system [42]. AD patients obtained a mean MMSE and GDS/FAST scores of 18.06 ± 3.36 and 4.17 ± 0.45 (mean $\pm$ SD), respectively. Controls had a mean MMSE and GDS/FAST scores of 28.88 ± 1.18 and 1.73 ± 0.45 points, respectively. No significant differences were observed in the mean age of both groups (p -value = 0.1911 > 0.05). Participants were not taking any medication (cholinesterase inhibitors, benzodiazepines or antidepressives) that could affect the MEG recordings at the time of study. Informed consent was obtained from all controls and all patients' caregivers. The study was approved by the local Research Ethics Committee.

2.2. MEG Recordings

Five minutes of spontaneous MEG activity were recorded for each subject using a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging), placed in a magnetically shielded room in the "Centro de Magnetoencefalografía Dr. Pérez-Modrego" of the Complutense University of Madrid. Subjects were asked to stay in a relaxed state, awake and with eyes closed during MEG acquisition. The recording equipment used in this study acquired the MEG signals at 678.17 Hz and implemented both a hardware band-pass filter between 1 Hz and 200 Hz, and a 50 Hz notch filter. The MEG data were then decimated by filtering the recordings with an anti-aliasing filter according to the Nyquist criterion and down-sampling by a factor of 4 to reduce the data length. The resulting sampling frequency was 169.54 Hz. Afterwards, the recordings were copied as ASCII files to a personal computer. Artifact-free epochs of length 5 s (848 samples) were selected for further analysis. Prior to time-frequency analysis, each MEG signal of 848 samples was digitally band-pass filtered with a Hamming window and cut-off frequencies at 0.5 and 40 Hz. According to the sampling theorem, the upper bound for the frequency components in our MEG signals (i.e., the Nyquist frequency) should be 84.77 Hz in order to avoid aliasing. Hence, it should be noticed that the proposed cut-off frequencies enable to retain the relevant spectral information in the MEG recordings. Figure 1 displays raw MEG epochs of 5 s from five sensors for an AD patient (Figure 1.a) and a control subject (Figure 1.b). The sensors correspond to central channels of five brain regions considered for topographic analyses (i.e. central region: 001; anterior region: 050; posterior: 083; left lateral region: 098; right lateral region: 109).

Figure 1. Raw MEG epochs of 5 s from central channels of five brain regions (i.e., central region: 001; anterior region: 050; posterior: 083; left lateral region: 098; right lateral region: 109). (a) AD patient. (b) Control subject.

3. METHODS

3.1. Spectral Parameters

A typical approach to characterize electromagnetic brain recordings consists in the analysis of their spectral content. In order to describe the properties of the power spectrum, several spectral parameters have been defined. They are based on the power spectral density (PSD) that represents how the power is distributed in the frequency domain. The Wiener-Khinchin-Einstein theorem states that PSD can be calculated as the Fourier transform of the autocorrelation function, since they are Fourier transforms pairs. In this work, the spectral estimation method provides a frequency resolution of 0.10 Hz. PSD is usually used as a useful and intuitive way to analyze the characteristics of a signal. Likewise, the spectral content between cut-off frequencies f_1 and f_2 was selected and PSD was normalized to a scale from 0 to 1, leading to the normalized PSD (PSD_n). It is noteworthy that f_1 and f_2 are the cut-off frequencies of the digital band-pass filter 0.5 and 40 Hz, respectively. After the normalization, PSD_n can be considered as a probability distribution. The following spectral parameters will be defined using this function.

3.1.1. Relative Power (RP)

The first parameter that we considered in the spectral analysis was relative power (RP). It represents the relative contribution of several oscillatory components to the global power spectrum. Thus, it is useful to analyze the changes in the spectral content of MEG recordings. Two advantages of relative power compared to absolute power are related to its ability to obtain both independent thresholds from the measurement equipment and lower inter-subject variability. Therefore, it has been recommended in previous EEG studies to

be employed to analyze dementia [43]. *RP* is obtained by summing the contribution of the desired spectral components. *RP* was calculated in the conventional EEG frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta 1 (13–19 Hz), beta 2 (19–30 Hz) and gamma (30–40 Hz). It is noteworthy that frequency boundaries were set taking into account that MEG recordings were filtered between 0.5 and 40 Hz.

3.1.2. Median Frequency (*MF*)

An alternative way to quantify the changes in the spectral content of MEG recordings is to calculate several characteristic frequencies that describe the behaviour of the most relevant oscillatory components. The median frequency (*MF*) offers a simple way of summarizing the whole spectral content of PSD. It is defined as the frequency which comprises 50% of the power. A parameter strongly related to *MF* is the mean frequency whose original definition is based on the computation of the spectral centroid. However, previous MEG studies have shown that *MF* provides a better performance to characterize the spectral changes associated with dementia than the mean frequency [22].

3.1.3. Individual Alpha Frequency (*IAF*)

The individual alpha frequency (*IAF*), also named peak frequency, quantifies the frequency at which the maximum alpha power is reached. Alpha oscillations are dominant in the EEG of resting normal subjects, with the exception of irregular activity in the delta band and lower frequencies [44]. This issue involves that PSD displays a peak around the alpha band. The estimation of *IAF* in the present work was based on the calculation of the median frequency in the extended alpha band (4–15 Hz), as previous MEG studies on dementia have recommended [22]. Thus, problems related to the appearance of several peaks in the considered frequency range or spurious spectral components can be avoided.

3.1.4. Spectral Entropy (*SE*)

Entropy is a thermodynamic function, which was adapted to the context of information theory. Its original definition implies uncertainty of information in terms of disorder, discrepancy and diversity. Powell and Percival introduced in 1979 an entropy definition where the irregularity in the signal was estimated in terms of the flatness of the power spectrum [45]. Thus, Shannon's entropy (*SE*) can be considered as a disorder quantifier [45]. A uniform power spectrum with a broad spectral content (e.g., a highly irregular signal like white noise) provides a high entropy value. On the contrary, a narrow power spectrum with only a few spectral components (e.g., a highly predictable signal like a sum of sinusoids) yields a low entropy value. In the present work, the definition of *SE* is based on Shannon's entropy computed over the normalized power spectrum. Moreover, *SE* was normalized to scale from 0 to 1.

3.2. Non-Linear Parameters

In order to complement the results provided by the spectral analyses, several non-linear methods were also applied. Increasing evidence suggests that ongoing oscillations in the brain may be weakly non-linear, which appears evident in the case of the alpha

rhythm [13]. Thus, non-linear methods have opened up a range of new perspectives for the study of normal and disturbed brain function [13, 27]. There is a wide variety of non-linear parameters. Traditionally used non-linear parameters, such as correlation dimension (D_2) and largest Lyapunov exponent ($L1$), require noise-free stationary data [46]. These theoretical limitations of D_2 and $L1$ involve that the characterization of spontaneous activity should be addressed using other nonlinear techniques suitable for noisy, non-stationary and high-dimensional data [27]. Due to this issue, in the present work, we selected the following non-linear parameters.

3.2.1. Sample Entropy (*SampEn*)

Sample entropy (*SampEn*) is an embedding entropy, which can be applied to short and relatively noisy time series [47]. *SampEn* was proposed by Richman and Moorman as an alternative to quantify the irregularity and reduce the bias introduced in the approximate entropy (*ApEn*) algorithm [47]. Thus, *SampEn* is largely independent of the sequence length and shows relative consistency under circumstances where *ApEn* does not [47]. *SampEn* is also a family of statistics, where two input parameters should be specified: a run length m and a tolerance window r . *SampEn* is the negative natural logarithm of the conditional probability that two sequences similar for m points remain similar at the next point [47]. In this work, *SampEn* was calculated with parameter values $m = 1$ and $r = 0.25$ times the SD of the original data sequence. Further details about the *SampEn* algorithm can be found in [47].

3.2.2. Lempel-Ziv Complexity (*LZC*)

In order to complement the description provided by the embedding entropy, two complexity measures were also used. The first one is Lempel-Ziv complexity (*LZC*), a non-parametric measure that evaluates the randomness of finite sequences, which could be also interpreted as a harmonic variability metric [48]. Complex data lead to high *LZC* values and regular sequences provide low *LZC* values. It is noteworthy that the signal must be coarse-grained, since the *LZC* algorithm analyzes a finite symbol sequence [49]. A binary (zeros and ones) conversion was used, as previous studies found that such conversion may retain enough signal information [49]. The detailed algorithm for the measure of *LZC* can be found in [49, 50].

3.2.3. Higuchi's Fractal Dimension (*HFD*)

Another nonlinear parameter useful to quantify the complexity of a given signal is fractal dimension (*FD*). The concept of *FD* was introduced by Mandelbrot to study temporal or spatial continuous phenomena that show correlation to a range of scales [51]. It can be interpreted as a quantifier of the complexity and self-similarity of a sequence [52]. Although many algorithms have been proposed to compute *FD*, such as those introduced by Maragos and Sun [53] or Katz [54], the Higuchi's fractal dimension (*HFD*) presents several advantages. *HFD* provides a more accurate estimation of the *FD* than those by other methods. In addition, *HFD* is simpler and faster than classical measures derived from chaos theory, like D_2 and $L1$, since *FD* is calculated directly from the time series. *HFD* is also more sensitive to the noise level than other measures,

leading to a sensible, slightly distorted translation towards higher FD values [52]. The detailed algorithm for the computation of HFD can be found in [55].

3.3. Statistical Analysis

Initially, a descriptive analysis was performed to analyze the characteristics of the dataset. However, variables did not meet homoscedasticity assumption. Therefore, Welch t -test was used for the statistical comparison between AD patients and control subjects. It is noteworthy that the statistical analysis was divided into two steps: (i) a descriptive statistical analysis to obtain a graphical description of the spatial distribution of significant differences, and (ii) a regional statistical analysis to accurately analyze the spatial patterns of statistical differences. In step (i), a descriptive statistical analysis was carried out to explore spatial differences between both populations, applying Welch t -test to each sensor. In the spectral analysis, the PSD_n was computed for each 5 s artifact-free MEG segment and results were averaged for each sensor. Spectral parameters were computed from this function to obtain a value per sensor and subject. Likewise, non-linear parameters were computed for each artifact-free epoch within the five-minute period of recording and averaged to obtain a value for each sensor and subject. In step (ii), spectral and non-linear parameters were averaged in five regions (anterior, central, left lateral, posterior and right lateral) and analyzed using Welch t -test with Bonferroni's correction. Figure 2 depicts the sensor-grouping [33, 40] which is included as default sensor groups in the 4D-Neuroimaging source analysis software.

Figure 2. Representation of sensor-grouping into five regions considered for topographic analyses: anterior, central, left lateral, posterior and right lateral.

The ability of the parameters to distinguish between the two groups was assessed by means of receiver operating characteristic (ROC) curves with a leave-one-out cross-validation procedure (LOO-CV). It is noteworthy that spectral and non-linear parameters were averaged for each region (anterior, central, left lateral, posterior and right lateral) to obtain a quantitative measure per subject and region. The averaged values were used as inputs to the ROC analysis. Optimum cut-off values were calculated for each ROC model in order to maximize the accuracy. Thus, they correspond to the point closest to the upper left corner of the ROC curve. The area under ROC curve (AUC) was employed as a global measure to summarize the diagnostic ability of each method. In addition, parameters whose AUC was higher than 0.780 were further analyzed in terms of sensitivity (i.e., percentage of patients with a correct AD diagnosis), specificity (i.e., proportion of healthy subjects properly detected) and accuracy (i.e., total fraction of AD patients and healthy subjects well classified).

Both statistical and classification analyses were performed using Matlab® (version 7.0; Mathworks, Natick, MA).

4. RESULTS

4.1. Spectral Parameters

First, the spectral content of AD patients' MEG activity was assessed using the relative power in the conventional frequency bands. Relative power values reflected a general increase in low frequency bands (delta and theta) and a general decrease in high frequency bands (beta1, beta2 and gamma). Detailed results for relative power values at each frequency band are shown in Figure 3, where the differences in the spatial distributions can be observed. Specifically, the analyses showed a significantly higher $RP(\text{delta})$ (central, left lateral and right lateral regions, $p < 0.05$; anterior region, $p < 0.01$) and $RP(\text{theta})$ (central, left lateral and posterior regions, $p < 0.01$; right lateral region, $p < 0.001$) in AD patients than controls. Also in AD patients, some lower tendencies were found in $RP(\text{alpha})$, though statistically significant only in the anterior region ($p < 0.05$). Significantly lower values over all brain regions in AD patients were found with $RP(\text{beta1})$ and $RP(\text{beta2})$ ($p < 0.05$; right lateral region, $p < 0.001$), whereas $RP(\text{gamma})$ exhibited some higher tendencies (anterior, left lateral and right lateral regions, $p < 0.05$).

The "shift-to-the-left" of the power spectrum was also analyzed by means of two additional spectral parameters: MF and IAF . Both parameters summarize the distribution of the PSD function, though the MF provides a global summary and the IAF is related to the dominant frequency of alpha frequency band. The distribution of the MF for each group and the corresponding p -values are presented in Figure 4, where AD patients exhibited significantly lower MF values than controls over all brain regions (central region, $p < 0.01$; anterior, left lateral, right lateral and posterior regions, $p < 0.001$). For IAF , Figure 5 depicts the distribution of the parameter for both groups and the corresponding p -values. Similar to MF , AD patients showed significantly lower IAF values than controls over all brain regions (anterior and posterior regions, $p < 0.01$; central, left lateral and right lateral regions, $p < 0.001$), though the statistical analyses with IAF demonstrated lower p -values than those with MF .

Figure 3. Spatial distribution of the mean relative power values at different frequency bands and the significant differences between the two groups: (a) $RP(\delta)$, (b) $RP(\theta)$, (c) $RP(\alpha)$, (d) $RP(\beta_1)$, (e) $RP(\beta_2)$, (f) $RP(\gamma)$.

The SE quantifies the irregularity of MEG activity in terms of the flatness of the power spectrum. The distribution of the SE for each group, together with the results of the spatial statistical analysis, is displayed in Figure 6. AD patients demonstrated significantly lower SE values than controls in anterior, central and right lateral regions

Figure 4. Spatial distribution of *MF* and its significant difference between the two groups.

Figure 5. Spatial distribution of *IAF* and its significant difference between the two groups.

Figure 6. Spatial distribution of *SE* and its significant difference between the two groups.

($p < 0.01$). Such results suggest a significant lower irregularity in AD patients' MEG activity in terms of the flatness of the power spectrum.

Finally, ROC curves with LOO-CV were generated to assess the performance of the spectral parameters in distinguishing between AD patients and control subjects. ROC curves for relative power values and the other spectral parameters (*MF*, *IAF* and *SE*) in all brain regions are displayed in Figures 7 and 8, respectively. In addition, classifications statistics using ROC curves with LOO-CV for parameters with AUC higher than 0.780 are summarized in Table 1. The highest accuracy was achieved by *SE* in the anterior region (82.3%, accuracy; 86.1%, sensitivity; 76.9%, specificity; 0.791, AUC), whereas the highest AUC was reached by *SE* in the right lateral region (75.8%, accuracy; 88.9%, sensitivity; 57.7%, specificity; 0.806, AUC). It is noteworthy that slightly lower accuracies and similar AUC values to those of *SE* were obtained by *RP(delta)* in the anterior region (80.7%, accuracy; 86.1%, sensitivity; 73.1%, specificity; 0.788, AUC) and *IAF* in the central region (80.7%, accuracy; 75.0%, sensitivity; 88.5%, specificity; 0.803, AUC).

Figure 7. ROC curves showing the performance of relative power, $RP(\delta)$, $RP(\theta)$, $RP(\alpha)$, $RP(\beta_1)$, $RP(\beta_2)$ and $RP(\gamma)$, in discriminating between AD patients and controls, and the corresponding AUC values for all brain regions (anterior, central, left lateral, posterior and right lateral).

4.2. Non-Linear Parameters

First, *SampEn* was calculated to measure the irregularity of the MEG activity. *SampEn* provides information about the fluctuations with time of the MEG signal, comparing the time series with a delayed version of itself [56]. Figure 9 depicts the distribution of *SampEn* for each group with the corresponding *p*-values. The analyses showed lower *SampEn* over all brain regions in AD patients than controls, suggesting that AD is accompanied with a higher MEG regularity. However, significant difference was only observed in the central region ($p < 0.05$).

In order to complement the results obtained by *SampEn*, two additional non-linear parameters were defined to quantify the complexity of MEG recordings. The first one is *LZC*. As mentioned previously, a binary conversion was performed for the

Figure 8. ROC curves showing the performances of *MF*, *IAF* and *SE* in discriminating between AD patients and controls, and the corresponding AUC values for all brain regions (anterior, central, left lateral, posterior and right lateral).

coarse-grained process and 20 s artifact-free epochs (3392 samples) were employed following the result of a previous study that *LZC* values become stable for MEG signals longer than 3000 samples [25]. Figure 10 presents the distributions of *LZC* values for both groups, as well as the corresponding *p*-values. The distributions of *LZC* values and significant difference followed a similar pattern as *SampEn*. Thus, AD patients demonstrated significant lower *LZC* values than controls over all brain regions (left lateral, right lateral and posterior regions, $p < 0.05$; anterior and central regions, $p < 0.01$), suggesting that AD is associated with a lower complexity of MEG activity.

The non-linear parameter *HFD* was calculated to provide an additional description of the complexity patterns of MEG recordings. It is noteworthy that an accurate estimation of *HFD* requires stationary MEG epochs. Thus, we applied the Bendat and Piersol's runs test [57] to assess the stationarity of the 5 s artifact-free epochs. We found that 57.41% of the epochs were weak or wide sense stationary. These epochs were then selected to compute *HFD*. The distributions of *HFD* for both groups and the corresponding *p*-values

Table 1. Classification statistics (sensitivity, specificity, accuracy and AUC) for the spectral parameters with AUC higher than 0.780

Parameter	Region	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
<i>RP(delta)</i>	Anterior	86.1	73.1	80.7	0.788
<i>RP(beta1)</i>	Anterior	75.0	76.9	75.8	0.791
<i>RP(beta1)</i>	Left lateral	77.8	73.1	75.8	0.782
<i>RP(beta1)</i>	Posterior	80.6	73.1	77.4	0.792
<i>RP(beta1)</i>	Right lateral	77.8	69.2	74.2	0.786
<i>MF</i>	Anterior	80.6	69.2	75.8	0.799
<i>MF</i>	Left lateral	66.7	42.3	56.5	0.803
<i>MF</i>	Posterior	83.3	61.5	74.2	0.797
<i>MF</i>	Right lateral	80.6	57.7	71.0	0.785
<i>IAF</i>	Anterior	72.2	76.9	74.2	0.787
<i>IAF</i>	Central	75.0	88.5	80.7	0.803
<i>IAF</i>	Left lateral	66.7	73.1	69.4	0.799
<i>IAF</i>	Right lateral	75.0	69.2	72.6	0.788
<i>SE</i>	Anterior	86.1	76.9	82.3	0.791
<i>SE</i>	Left lateral	91.7	61.5	79.0	0.795
<i>SE</i>	Right lateral	88.9	57.7	75.8	0.806

Figure 9. Spatial distribution of *SampEn* and its significant difference between the two groups.

Figure 10. Spatial distribution of *LZC* and its significant difference between the two groups.

in Figure 11 show that AD patients exhibit significant lower *HFD* values than controls over all brain regions except the left lateral region where only some decreasing tendencies were observed (right lateral and posterior, $p < 0.05$; anterior and central regions, $p < 0.01$).

Figure 11. Spatial distribution of *HFD* and its significant difference between the two groups.

ROC curves for the non-linear parameters (*SampEn*, *LZC* and *HFD*) in all brain regions are displayed in Figure 12. In addition, classifications statistics using ROC curves with LOO-CV for parameters with AUC higher than 0.780 are shown in Table 2. The highest accuracy was achieved by *LZC* in the left lateral region (79.0%, accuracy;

Figure 12. ROC curves showing the performances of *SampEn*, *LZC* and *HFD* in discriminating between AD patients and controls, and the corresponding AUC values for all brain regions (anterior, central, left lateral, posterior and right lateral).

Table 2. Classification statistics (sensitivity, specificity, accuracy and AUC) for the non-linear parameters with AUC higher than 0.780

Parameter	Region	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
<i>LZC</i>	Left lateral	83.3	73.1	79.0	0.787
<i>LZC</i>	Right lateral	86.1	61.5	75.8	0.780
<i>HFD</i>	Anterior	86.1	65.4	77.4	0.781
<i>HFD</i>	Left lateral	88.9	57.7	75.8	0.783

83.3%, sensitivity; 73.1%, specificity; 0.787, AUC), though it was still lower than that of *SE* in the anterior region. Moreover, lower classification statistics were achieved by *HFD* in the anterior region (77.4%, accuracy; 86.1%, sensitivity; 65.4%, specificity; 0.781, AUC) in comparison to *LZC*.

5. DISCUSSION

In this work, the performance of several spectral and non-linear parameters in characterizing spontaneous MEG activity of 36 AD patients and 26 healthy subjects was tested. Our findings suggest that AD affects spontaneous MEG activity by increasing slow rhythms and decreasing fast oscillations. On the other hand, statistically significant decreases were observed in spectral and non-linear entropies in AD patients, suggesting that AD is associated with an increased regularity. Likewise, complexity quantifiers are significantly lower in AD patients than controls, suggesting that AD causes a loss of complexity in spontaneous MEG rhythms. ROC analysis showed classification statistics with accuracies and AUCs of around 80% and 0.800, respectively.

Further inspection of relative power values reveals that AD patients reached significantly higher *RP* values in low frequency bands and significantly lower *RP* values in high frequency bands than controls. These findings suggest that AD is associated with a slowing of spontaneous MEG activity, in agreement with results from previous investigations [15, 17, 18, 20]. The significant “shift-to-the-left” of the power spectrum in AD was also observed by means of *MF* and *IAF*. These spectral parameters are significantly lower in AD patients than controls, in agreement with previous studies [16, 22]. Spatial patterns of significant differences also agree with those reported in previous MEG studies, where AD patients exhibited higher absolute low frequency with a fronto-central maximum and a lower high frequency power values over the occipital and temporal areas in comparison with healthy controls [15].

Similar spatial distributions of abnormalities were obtained by previous MEG studies performing source analysis. Fernández *et al.* [58, 59] reported a significant increase in the dipole density of slow-wave activity in temporo-parietal regions, which agrees with the results of Osipova *et al.* that the strongest activation in theta band in the right temporal region [23] and parieto-occipital deficits [16] was observed in AD patients. The results of Osipova *et al.* [23] support the hemispheric asymmetry in the

spatial patterns of significant differences that we observed with $RP(\theta)$, $RP(\beta_1)$ and $RP(\beta_2)$ in AD patients. Specifically, our findings suggest that the right lateral region is slightly more affected by dementia than the left lateral one. Some investigations indicate that the predominance of AD in the right hemisphere is associated with a significant impairment in cognitive function [60]. It is noted that our AD patients were of moderate to severe degree of dementia. Therefore, a right hemispheric predominance in the patterns of significant differences is expected. The lack of significant differences in the alpha band in the posterior areas can be also related to the moderate to severe cognitive impairment of the participating AD patients. Similar results were also reported in previous MEG studies where the alpha band did not show significant differences [18, 20]. Likewise, the significant changes of $RP(\alpha)$ in the anterior area is consistent with single dipole source analyses of EEG data, which suggest that alpha and beta activities in the anterior area are affected as a function of AD severity [61].

There is long standing evidence suggesting that the cholinergic deficit plays a critical role in the EEG slowing associated with AD [12]. Analogously, some findings support that MEG slowing in AD could also be due to the loss of neurotransmitter acetylcholine, since the cholinergic system modulates spontaneous cortical activity at theta and alpha bands and functional coupling in the theta band [62]. Source analyses of MEG signals revealed that AD is accompanied with a higher dipole density at delta and theta bands [58, 59], which suggests that MEG slowing in AD might be due to an increase in activation of low frequency generators, rather than the slowing of existing sources [16]. Further research is needed to confirm these hypotheses.

Spectral and non-linear parameters that quantify the irregularity of MEG recordings also provided significant results. Statistical analyses of SE and $SampEn$ suggest a significantly lower irregularity of MEG activity in AD patients, mainly concentrated in the centro-temporal regions. Similar spatial patterns of significant differences were observed in previous MEG studies that reported a lateralization of the reduction in entropy. Specifically, previous analyses using several spectral entropies (Shannon, Tsallis and Rényi entropy) suggested that the most significant differences between AD patients and controls were observed in both lateral cerebral regions, though the right one exhibited slightly lower p -values than the left one [33]. This result is related to the hemispheric asymmetry of RP values and supports the notion that AD patients in our study have moderate to severe cognitive impairment. Our findings are in agreement with previous MEG studies reporting a global decrease in irregularity associated with AD found using several spectral entropies [22, 32] and non-linear irregularity quantifiers [26, 27, 29, 32, 34].

Regarding the non-linear parameters that quantify the complexity of MEG recordings, our findings show significantly lower LZC and HFD values in AD patients than controls. Significant differences were mainly in anterior and central regions, though posterior and right lateral regions also achieved statistically significant results. Previous MEG studies also reported a loss of complexity associated with AD using several non-linear parameters [25–29, 31]. A similar pattern of abnormalities was reported in an MEG study using HFD , where the highest classification accuracies were

found in the anterior, central and right lateral regions [30]. Analogous to spectral parameters, non-linear parameters exhibited a hemispheric asymmetry in the patterns of significant differences. Our *HFD* results showed lower *p*-values in the right lateral region than in the left lateral one, reflecting the moderate to severe cognitive deficit of the AD patients in our study.

Owing to the different natures of the parameters, the decrease in irregularity and complexity should be interpreted from two points of view. The spectral parameter (i.e., *SE*) suggests that AD is accompanied with a loss of frequency components. Thus, the spectral content of AD patients' MEG activity is more uniform than controls. The change in information entropy within the EEG may reflect a real variation in cortical functional organization [63]. Therefore, the decrease in irregularity can be associated with both loss of information content [64] and decrease in information processing at the cerebral cortex [63]. Closely related to the previous idea, the decrease in irregularity and complexity demonstrated by non-linear parameters (i.e., *SampEn*, *LZC* and *HFD*) could be partially explained by a decrease of dynamical complexity in some parts of the brain. Diverse mechanisms have been proposed to explain these abnormalities in the electromagnetic brain activity. The analyses with various non-linear parameters, such as *D₂*, *L1*, neural complexity and multiscale entropy, revealed that brain dynamics in AD are characterized by a decrease in complexity of the electromagnetic brain activity [31, 65, 66], which could be related to a degradation in the flexibility of the brain to process information [67]. Likewise, AD has been described as a disconnection syndrome, where the interactions between brain regions are strongly affected by anatomical disconnections among different cortical regions [68] or reduced cholinergic coupling interactions between cortical neurons [12]. On the basis of the previous findings, some studies hypothesized that the decrease in dynamical complexity could be due to neuronal death, a general effect of neurotransmitter deficits or loss of connectivity of local neural networks [12, 13]. On the other hand, some studies suggested that the loss of complexity associated with AD may be frequency-dependent and may be influenced by the pattern of increases and decreases of functional connectivity [31, 41]. Certainly, further research should be conducted to assess the role of specific frequency bands in the complexity patterns usually associated with AD.

Further inspection of results shows that the *SE* reached both the highest accuracy (82.3%) in the anterior region and the highest AUC in the right lateral region (0.806). Similar AUCs and slightly lower accuracies were obtained by *RP(delta)* in the anterior region (80.7%, accuracy; 0.788, AUC) and *IAF* in the central region (80.7%, accuracy; 0.803, AUC). The *LZC* in the left lateral region had an accuracy and an AUC similar to the aforementioned parameters (79.0% and 0.787, respectively). Our results suggest that spectral parameters provide more information than nonlinear parameters in characterizing brain dynamics. There is little evidence that non-linear parameters are better suited to discriminate between AD patients and controls than spectral methods. Spectral and non-linear methods can yield complementary information useful to improve the accuracy in AD diagnosis [22, 32]. It is noteworthy that both spectral and non-linear parameters achieved classification statistics favorably comparable with those reported in previous MEG studies [20, 27, 29, 32, 40]. Although the accuracies reported

in some published works were higher than 80.7%, comparisons should be established with caution considering the small sample sizes [22, 25, 27, 30, 32–34].

Some methodological and clinical findings of our study merit further consideration. None of the patients were taking any medication which could affect MEG activity during the study. Therefore, it is impossible that the abnormal slowing, irregularity and complexity patterns found in our patients could be drug-related. However, other neurodegenerative diseases, such as mild cognitive impairment and vascular dementia, etc., also elicit similar abnormal patterns in EEG and MEG activity. Further research should be conducted to compare different patterns of abnormalities associated with these disorders. It is worth mentioning that the applied statistical methodology is adequate to draw accurate statistical conclusions regarding the spatial distribution of significant differences. However, magnetic activity outside the head is mainly generated by tangential currents [10]. An acquisition sensor is most sensitive to current generators that are peripheral to the sensor area. Therefore, a source analysis could be performed to avoid an erroneous interpretation of findings derived from spatial patterns.

6. CONCLUSION

There is increasing evidence that AD is associated with a slowing of brain rhythms, together with a decrease in irregularity and complexity of the brain networks. Our findings support that AD elicits an abnormal brain dynamics. Furthermore, our results revealed that different spatial patterns of abnormalities detected by different spectral and nonlinear parameters are present in MEG activity of AD patients and control subjects. The classification statistics suggest that both spectral and non-linear parameters can be useful in discriminating between AD patients and healthy controls. These parameters may lead to a better understanding of the underlying brain dynamics in AD and can provide useful descriptors to characterize the spontaneous MEG activity in AD.

ACKNOWLEDGEMENTS

This work was supported in part by “Ministerio de Ciencia e Innovación” under projects TEC2008-02241 and TEC2011-22987. The authors would like to thank the “Centro de Magnetoencefalografía Dr. Pérez-Modrego” of the Complutense University of Madrid for supplying the MEG recordings analyzed in this study.

CONFLICT OF INTEREST

The authors indicated no potential conflicts of interest.

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