34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Synchrony analysis of spontaneous MEG activity in Alzheimer's disease patients

Carlos Gómez*, *Member, IEEE*, Mario Martínez-Zarzuela, Jesús Poza, *Member, IEEE*, Francisco J. Díaz-Pernas, Alberto Fernández, and Roberto Hornero, *Senior Member, IEEE*

***Abstract*— The aim of this study was to analyze the magnetoencephalography (MEG) background activity in Alzheimer's disease (AD) patients using cross-approximate entropy (*Cross-ApEn*). *Cross-ApEn* is a nonlinear measure of asynchrony between time series. Five minutes of recording were acquired with a 148-channel whole-head magnetometer in 12 AD patients and 12 age-matched control subjects. We found significantly higher synchrony between MEG signals from AD patients compared with control subjects. Additionally, we evaluated the ability of *Cross-ApEn* to discriminate these two groups using receiver operating characteristic (ROC) curves with a leave-one-out cross-validation procedure. We obtained an accuracy of 70.83% (66.67% sensitivity, 75% specificity) and a value of area under the ROC curve of 0.83. These results provide evidence of disconnection problems in AD. Our findings show the usefulness of *Cross-ApEn* to detect the brain dysfunction in AD.**

I. Introduction

ALZHEIMER'S DISEASE (AD) is a primary degenerative neurological disorder of unknown etiology that gradually destroys brain cells. Nowadays, it is considered the main cause of dementia in western countries [1]. AD affects 1% of population aged 60-64 years, but the prevalence increases exponentially with age, so about 30% of people over 85 years suffer from this disease [2]. Additionally, as life expectancy has improved significantly in the last decades, it is expected that the number of people with dementia increase up to 81 millions in 2040 [2]. Clinically, this disease manifests as a slowly progressive impairment of mental functions whose course lasts several years prior to death [2]. Usually, AD starts by destroying neurons in parts of the patient's brain that are responsible for storing and retrieving information. Then, it affects the brain areas involved in language and reasoning. Eventually, many other brain regions are atrophied. Although a definite AD diagnosis is only possible by necropsy, a differential diagnosis with other types of dementia and with major depression should be attempted. The differential diagnosis includes medical history studies, physical and neurological evaluation, mental status tests, and neuroimaging techniques.

Nowadays, magnetoencephalography (MEG) recordings are not used in AD clinical diagnosis, in spite of its potential as aid diagnostic tool. MEG is a non-invasive technique that records the electromagnetic fields produced by brain activity with good temporal resolution. MEG technology offers some advantages over electroencephalography (EEG). For instance, magnetic fields are not distorted by the resistive properties of the skull. Furthermore, EEG signals are influenced by a wide variety of factors, such as distance between sensors, electrode location, reference point or conducting substance between skin and electrode. 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, MEG signals must be recorded in a magnetically shielded room. Thus, MEG is characterized by limited availability and high equipment cost.

Entropy is a concept addressing randomness and predictability, with greater entropy often associated with more randomness and less system order [3]. Mainly, there are two families of entropy estimators: spectral entropies and embedding entropies [4]. Spectral entropies extract information from the amplitude component of the frequency spectrum. On the other hand, embedding entropies are calculated directly using the time series. This entropies family provides information about how the signal fluctuates with time by comparing the time series with a delayed version of itself [4]. Both spectral and embedding entropies have demonstrated their usefulness in the analysis of EEG/MEG background activity in AD. An increase of entropy values has been found using approximate entropy (*ApEn*) [5], sample entropy [6], Shannon spectral entropy, Rényi spectral entropy and Tsallis spectral entropy [7]. However, all these measures are applied to each EEG or MEG channel independently. In the current study, we want to go a step ahead, applying cross-approximate entropy (*Cross-ApEn*) to MEG recordings from 12 AD patients and 12 age-matched control subjects. *Cross-ApEn* is a nonlinear measure of asynchrony between time series. It has already been used to study some biological signals, as hormone time series dynamics [8], blood oxygen saturation and heart rate [9].

The purpose of this study was to test the hypothesis that

Manuscript received March 29, 2012. This research was supported in part by the "Ministerio de Economía y Competitividad" under project TEC2011-22987, the Proyecto Cero 2011 on Ageing from Fundación General CSIC, and project VA111A11-2 from Consejería de Educación (Junta de Castilla y León). *Asterisk indicates corresponding author*.

C. Gómez, J. Poza, and R. Hornero are with the Biomedical Engineering Group at Department of Signal Theory and Communications, E.T.S. Ingenieros de Telecomunicación, University of Valladolid, Campus Miguel Delibes, 47011 – Valladolid, Spain (e-mail: cargom@tel.uva.es).

M. Martínez-Zarzuela and F. J. Díaz-Pernas are with the Industrial Telematics Group, University of Valladolid, Spain.

A. Fernández is with the Centre for Biomedical Technology, Technical University of Madrid, Spain.

Cross-ApEn values 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. MEG recording

MEGs were recorded using 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. They were asked to stay awake and to avoid eye and head movements. For each subject, five minutes of recording were acquired at a sampling frequency of 678.17 Hz. These recordings were down-sampled by a factor of four, obtaining a sampling rate of 169.55 Hz. Data were digitally filtered between 0.5 and 40 Hz. Finally, artifact-free epochs of 5 seconds (848 samples) were selected.

B. Subjects

The MEG data were acquired from 24 subjects. Twelve patients (3 men and 9 women) fulfilling the criteria of probable AD (age = 70.42 ± 9.04 years, mean ± standard deviation SD) have participated in the present study. The patients were diagnosed according to the criteria of the National Institute of Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA). The MMSE score was 17.00 ± 3.98 (Mean ± SD). None of the patients used any kind of medication that could have an influence on the MEG.

MEGs were also obtained from 12 age-matched control subjects (5 men and 7 women, age = 70.42 ± 7.75 years, MMSE = 29.50 ± 0.52, mean ± SD). The local ethics committee approved the study. All control subjects and all caregivers of the demented patients gave their informed consent for the participation in the current research.

C. Cross Approximate Entropy (Cross-ApEn)

Cross-ApEn is a two-parameter family of statistics introduced as a measure of asynchrony between two paired time series [10]. It evaluates secondary as well as dominant patterns in data, quantifying changes in underlying episodic behavior that do no reflect in peak occurrences and amplitudes [8]. To compute *Cross-ApEn*, two input parameters must be specified: a run length m and a tolerance window r. For two time series, $u(i)$ and $v(i)$, *Cross-ApEn* measures, within tolerance r, the (conditional) regularity or frequency of v-patterns similar to a given u-pattern of window length m. Although m and r are critical in the calculation of *ApEn* and *Cross-ApEn*, no guidelines exist to optimize their values. However, values of m equal to 1 or 2, and r between 0.1 and 0.25 has been suggested [10]. In this pilot study, we have chosen $m = 1$ and $r = 0.2$ to compute *Cross-ApEn*.

Given two equally sampled sequences of length N, $u = [u(1), u(2),\ldots, u(N)]$ and $v = [v(1), v(2),\ldots, v(N)]$, the algorithm to compute *Cross-ApEn* is the following [9, 10]:

1) Normalize $u(i)$ and $v(i)$. The normalized time series $u^*(i)$ and $v^*(i)$ are:
$$u^*(i) = \left[u(i) - \text{mean}(u)\right]/\text{SD}(u) \quad (1)$$
$$v^*(i) = \left[v(i) - \text{mean}(v)\right]/\text{SD}(v) \quad (2)$$
2) Form the vector sequences $x(i) = [u^*(i), u^*(i+1),\ldots, u^*(i+m-1)]$ and $y(j) = [v^*(j), v^*(j+1),\ldots, v^*(j+m-1)]$. These vectors represent m consecutive u^* and v^* values starting with the ith and jth point, respectively.
3) Define the distance between $x(i)$ and $y(j)$, $d[x(i), y(j)]$, as the maximum absolute difference of their corresponding scalar components:
$$d[x(i), y(j)] = \max_{k=1,2,\ldots m} \left|u(i+k-1) - v(j+k-1)\right| \quad (3)$$
4) For each $x(i)$, count the number of j ($j=1,2,\ldots,N-m+1$) so that $d[x(i), y(j)] \le r$, denoted as $N_i^m(r)$. Then, for $i=1,2,\ldots,N-m+1$, set
$$C_i^m(r)(v\|u) = \frac{N_i^m(r)}{N-m+1} \quad (4)$$
5) Compute the natural logarithm of each $C_i^m(r)$ and average it over i:
$$\phi^m(r)(v\|u) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1} \ln C_i^m(r)(v\|u) \quad (5)$$
6) Finally, *Cross-ApEn* is defined by:
$$Cross\text{-}ApEn(m,r,N)(v\|u) = \phi^m(r)(v\|u) - \phi^{m+1}(r)(v\|u) \quad (6)$$

It is important to note that *Cross-ApEn* is not always defined because $C_i^m(r)(v||u)$ may be equal to 0 in the absence of similar patterns between u and v. To solve this, two correction strategies have been proposed [11]: *bias 0* and *bias max*. In this study, both correction strategies have been applied. Both strategies assign non zero values to $C_i^m(r)(v||u)$ and $C_i^{m+1}(r)(v||u)$ in the absence of matches, as follows:

1) *Bias 0*: $C_i^m(r) = C_i^{m+1}(r) = 1$ if originally $C_i^m(r) = C_i^{m+1}(r) = 0$, and $C_i^{m+1}(r) = (N-m)^{-1}$ if originally $C_i^m(r) \neq 0$ and $C_i^{m+1}(r) = 0$.
2) *Bias max*: $C_i^m(r) = 1$ if originally $C_i^m(r) = 0$, and $C_i^{m+1}(r) = (N-m+1)^{-1}$ if originally $C_i^{m+1}(r) = 0$.

III. Results

Cross-ApEn algorithm was applied to the MEG recordings with parameter values of $m = 1$ and $r = 0.2$ and both correction strategies *bias 0* and *biax max*. The end result of computing *Cross-ApEn* for all pair-wise combinations of MEG channels is a $B \times B$ matrix with $B = 148$ (number of channels), where each entry $B_{i,j}$ contains the *Cross-ApEn* value for channels i and j. It is important to note that there is a direction dependence, due to the fact that $\phi^m(r)(v||u)$ will note generally be equal to $\phi^m(r)(u||v)$. This may be considered an advantage over other synchrony methods as coherence or synchronization likelihood. Fig. 1 and 2 summarize the average *Cross-ApEn* values estimated at both groups for all the pair-wise combinations of MEG

channels using *bias 0* and *bias max* corrections, respectively. This figures show that entropy values were lower in the AD group than in the control group for all channels combinations, which suggests that this disorder is accompanied by a MEG asynchrony decrease. Differences between patients and controls were statistically significant (Student's *t*-test) in 55.69% of the 148 × 148 MEG combinations using *bias 0* correction, and in 63.66% using *bias max* correction. As a multiple comparison correction has not been performed, these results should be taken with caution.

Furthermore, we evaluated the ability of *Cross-ApEn* to discriminate AD patients from elderly control subjects by means of receiver operating characteristic (ROC) curves. A ROC curve is a graphical representation of the trade-offs between sensitivity and specificity. We define sensitivity as the rate of ADHD patients who test positive, whereas specificity represents the fraction of controls correctly recognized. Accuracy quantifies the total number of subjects precisely classified. The area under the ROC curve (AROC) is a single number summarizing the performance. AROC indicates the probability that a randomly selected AD patient has a *Cross-ApEn* value lower than a randomly chosen control subject. In order to calculate these values, a leave-one-out cross-validation procedure was used. In the leave-one-out method, the data from one subject are excluded from the training set one at a time and then classified on the basis of the threshold calculated from the data of all other subjects. The leave-one-out cross-validation procedure provides a nearly unbiased estimate of the true error rate of the classification procedure. To simplify the analyses, we calculate the mean value of all the 148 × 148 *Cross-ApEn* values, for *bias 0* and *bias max* corrections. For both correction strategies, we obtained the same accuracy (70.83%), sensitivity (66.67%), specificity (75.00%) and AROC (0.83) values.

IV. Discussion and Conclusions

We analyzed the MEG background activity from 12 AD patients and 12 control subjects by means of *Cross-ApEn*. Our purpose was to test the hypothesis that the brain activity recorded in MEG signals can reflect a disconnection syndrome in AD patients.

Cross-ApEn has proven to be effective in discriminating AD patients from controls. Our study revealed that AD subjects have lower connectivity/asynchrony values. Our findings support the notion that AD involves a loss of functional connectivity. Moreover, significant statistical differences were found in several combinations of MEG channels. However, these findings are preliminary and require replication in a larger patient population before any conclusion can be made about the clinical diagnostic value of this measure.

Several studies have shown the loss of brain connectivity in AD using EEG and MEG recordings. Most of these studies were carried out using the well-known coherence [12]. The main finding is a lower synchronization level in alpha and beta frequency bands. Nevertheless, contradictory results have been found in the other frequency bands [2]. More recently, other connectivity methods have been used to analyze the brain activity in AD, as cross mutual information [13], global field synchronization [14], and synchronization likelihood [15]. For instance, Jeong *et al.* [13] found that cross mutual information in EEGs from AD patients was lower than in normal controls, especially over frontal and

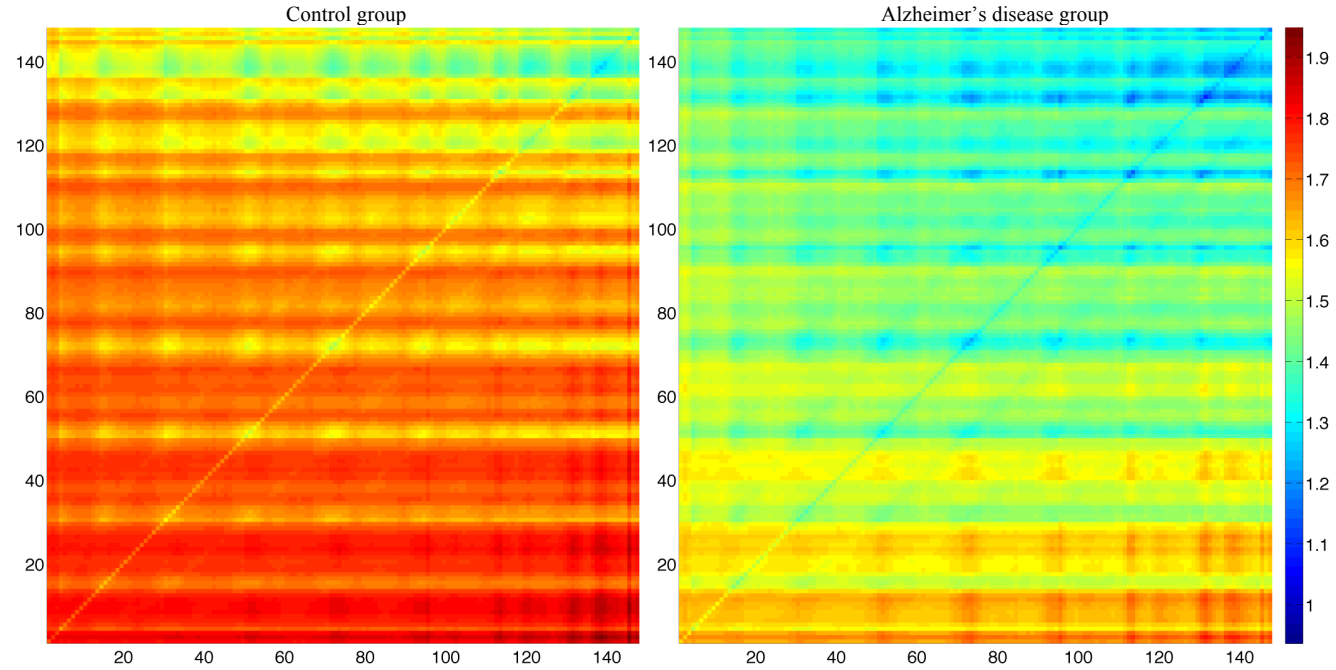

Fig. 1. Average *Cross-ApEn* values with *bias 0* correction for AD and control groups.

antero-temporal brain regions. Using global field synchronization, similar results were found: patients showed decreased synchronization values in almost all frequency bands [14]. These results may confirm the hypothesized disconnection syndrome. This connectivity loss in AD may be due to the fact that neuritic plaques appears organized in AD patients' brains, affecting the ends of corticocortical connections [16].

ROC curves were used to assess the ability of *Cross-ApEn* to classify ADHD patients and control subjects. We reached an accuracy of 70.83% (66.67% sensitivity, 75% specificity) and a value of area under the ROC curve of 0.83. Nevertheless, these values should be taken with caution due to the small sample size.

In sum, our study leads us to conclude that MEG background activity in AD patients is accompanied by a brain asynchrony decrease. The results obtained with *Cross-ApEn* showed significant differences between AD patients and controls, indicating an abnormal type of dynamics associated with this disorder.

REFERENCES

[1] T. D. Bird, "Alzheimer's disease and other primary dementias," in *Harrison's principles of internal medicine*, E. Braunwald, A. S. Fauci, D. L. Kasper, S. L. Hauser, D. L. Longo, and J. L. Jameson, Eds. New York: The McGraw-Hill Companies Inc, 2001, pp. 2391–2399.

[2] J. Jeong, "EEG dynamics in patients with Alzheimer's disease," *Clin. Neurophysiol.*, vol. 115, pp. 1490–1505, 2004.

[3] D. Abásolo, R. Hornero, P. Espino, J. Poza, C. I. Sánchez, and R. de la Rosa, "Analysis of regularity in the EEG background activity of Alzheimer's disease patients with approximate entropy," *Clin. Neurophysiol.*, vol. 116, no. 8, pp. 1826–1834, Aug. 2005.

[4] J. W. Sleigh, D. A. Steyn-Ross, C. Grant, and G. Ludbrook, "Cortical entropy changes with general anaesthesia: theory and experiment," *Physiol. Meas.*, vol. 25, no. 4, pp. 921–934, Aug. 2004.

[5] R. Hornero, J. Escudero, A. Fernández, J. Poza, and C. Gómez, "Spectral and non-linear analyses of MEG background activity in patients with Alzheimer's disease," *IEEE Trans. Biomed. Eng.*, vol. 55, pp. 1658–1665, 2008.

[6] C. Gómez, R. Hornero, D. Abásolo, A. Fernández, and J. Escudero, "Analysis of MEG background activity in Alzheimer's disease using non-linear methods and ANFIS," *Ann. Biomed. Eng.*, vol. 37, pp. 586–594, 2009.

[7] J. Poza, R. Hornero, J. Escudero, A. Fernández, and C. I. Sánchez, "Regional analysis of spontaneous MEG rhythms in patients with Alzheimer's disease using spectral entropies," *Ann. Biomed. Eng.*, vol. 36, pp. 141–152, 2008.

[8] J. D. Veldhuis, S. M. Pincus, M. C. García-Rudaz, M. G. Ropelato, M. E. Escobar, and M. Barontini, "Disruption of the joint synchrony of luteinizing hormone, testosterone, and androstenedione secretion in adolescents with polycystic ovarian syndrome," *J. Clin. Endocrinol. Metab.*, vol. 86, pp. 72–79, 2001.

[9] D. Álvarez, R. Hornero, D. Abásolo, F. del Campo, C. Zamarrón, and M. López, "Nonlinear measure of synchrony between blood oxygen saturation and heart rate from nocturnal pulse oximetry in obstructive sleep apnoea syndrome," *Physiol. Meas.*, vol. 30, pp. 967–982, 2009.

[10] S. M. Pincus, "Irregularity and asynchrony in biologic network signals," *Methods Enzymol.*, vol. 321, pp. 149–82, 2000.

[11] J. S. Richman and J. R. Moorman, "Physiological time series analysis using approximate entropy and sample entropy," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 278, pp. H2039−2049, 2000.

[12] P. L. Nunez, R. Srinivasan, A. F. Westdorp, R. S. Wijesinghe, D. M. Tucker, R. B. Silberstein, and P. J. Cadusch, "EEG coherency. I: Statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and interpretation at multiple scales," *Electroencephalogr. Clin. Neurophysiol.*, vol. 103, no. 5, pp. 499–515, 1997.

[13] J. Jeong, J. C. Gore, and B. S. Peterson, "Mutual information analysis of the EEG in patients with Alzheimer's disease," *Clin. Neurophysiol.*, vol. 112, no. 3, pp. 827–835, 2001.

[14] T. Koenig, L. Prichep, T. Dierks, D. Hubl, L. O. Wahlund, E. R. John, and V. Jelic, "Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment," *Neurobiol. Aging*, vol. 26, no. 2, pp. 165–171, 2005.

[15] C. J. Stam, B. F. Jones, I. Manshanden, A. M. van Cappellen van Walsum, T. Montez, J. P. A. Verbunt, J. C. de Munck, B. W. van Dijk, H. W. Berendse, and P. Scheltens, "Magnetoencephalographic evaluation of resting-state functional connectivity in Alzheimer's disease," *Neuroimage*, vol. 32, no. 3, pp. 1335–1344, 2006.

[16] M. C. de LaCoste and C. L. White, "The role of cortical connectivity in Alzheimer's disease pathogenesis: a review and model system," *Neurobiol. Aging*, vol. 14, no. 1, pp. 1–16, 1993.

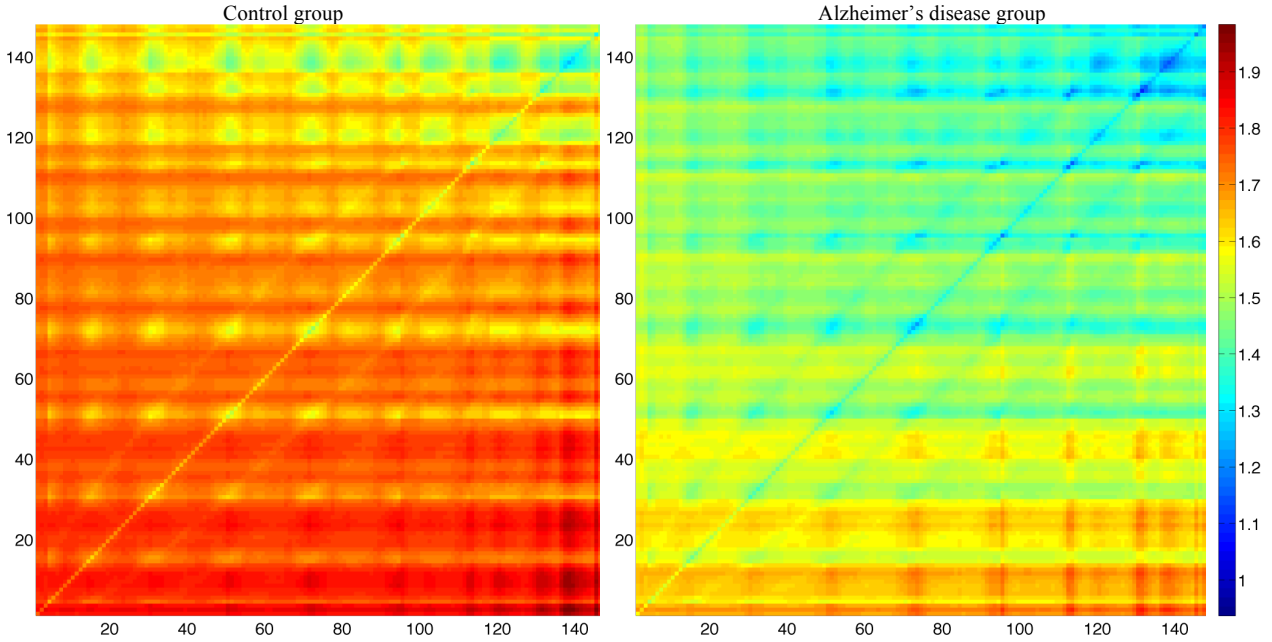

Fig. 2. Average *Cross-ApEn* values with *bias max* correction for AD and control groups.