Analysis of Spontaneous MEG Activity in Patients with Alzheimer's Disease using Spectral Entropies

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Abstract—The aim of this study was to explore the ability of several spectral entropies to discriminate between spontaneous magnetoencephalographic (MEG) oscillations from 20 Alzheimer's disease (AD) patients and 21 controls. Hence, the relative spectral power (*RSP*) in classical frequency bands was calculated from the averaged power spectral density. Given the fact that the *RSP* can be viewed as a probability distribution function, the Shannon spectral entropy, Tsallis spectral entropy, generalized escort-Tsallis spectral entropy and Rényi spectral entropy were calculated from the *RSP*. Significant differences for each parameter were assessed with Mann-Whitney U test, whereas classification performance was studied using binary logistic regression. Results revealed an increase in the *RSP* of control subjects at beta and gamma bands, while AD patients showed an increase in the *RSP* values at delta and theta bands. Entropic quantifiers obtained statistically significant lower values for AD patients than for controls. This issue suggests a significant decrease in irregularity of AD patients' MEG activity.

I. INTRODUCTION

ALZHEIMER'S disease (AD) is a primary degenerative dementia that gradually destroys brain cells and leads to progressive decline in mental function [1]. Differential diagnosis of AD is based on a complete medical evaluation. Nevertheless, the accuracy of clinical diagnosis is about 90% [2]. It can be confirmed only by histological examination of brain tissue.

In order to improve the diagnosis, electroencephalographic (EEG) brain activity has been widely analyzed. More recently, special attention has also been paid to magnetoencephalographic (MEG) activity. Both recordings are generated by synchronous oscillations of pyramidal neurons. However, EEG is sensitive to all primary currents, while MEG is insensitive to current flows oriented perpendicularly to the scalp. Since EEG and MEG detect slightly different features of the electromagnetic brain activity, they can be viewed as complementary techniques [3]. An important advantage of MEG over EEG arises from

the insensitivity of magnetic fields to inhomogeneities in the head. This implies that MEG recordings are less distorted than EEG signals on the scalp [3].

Some abnormalities in moderate and severe AD patients' EEG and MEG background activity have been observed [4], [5]. Whereas the EEG has been broadly investigated using spectral and non-linear measures, only a few studies have analyzed the MEG patterns in AD. In this way, spontaneous MEG activity shows increased slow rhythms and reduced fast activity in AD patients in comparison with healthy subjects [6]–[8]. This fact has also been observed using some spectral parameters like mean frequency [9], [10] and individual alpha peak [7], [10], [11]. From another point of view, studies analyzing MEG recordings at rest showed a global decrease in irregularity [10] and complexity [12] when AD patients are compared with healthy controls. However, some authors only reported the loss of complexity in the high frequencies [13]. Other approaches, which focused on analyzing the functional connections rather than local abnormalities in AD, have found both a decrease of coherence values in the alpha band [14] and a general decrease of coherence in all frequency bands [6]. A lower level of synchronization has also been reported in the upper alpha, beta and gamma bands of AD patients in comparison with controls, suggesting a loss of functional connectivity [15]. Recently, it has been observed that resting-state functional connectivity in AD is characterized by specific changes of long and short distance interactions in several frequency bands [16]. Therefore, it can be inferred that AD is related with an abnormal function of the large scale brain networks [16].

In this scenario, where highly nonlinear and long-range (for interneural distances) phenomena are present, a non-extensive analysis of the problem may be appropriate. In a similar context, previous studies have successfully applied several quantifiers based on extensive (Shannon) and non-extensive (Tsallis, generalized escort-Tsallis and Rényi) information measures to analyze EEG signals [17]–[20]. These non-extensive measures are controlled by the parameter q , which is modified to emphasize particular characteristics of the associated dynamics.

This study is a first approach to explore the ability of several measures from information theory to characterize MEG rhythms in AD. The proposed parameters are entropies based on the relative power distribution. Firstly, the Fourier transform (FT) was used to compute the power spectral density (PSD) for each MEG recording from AD patients and controls. Relative spectral power (*RSP*), Shannon spectral entropy (*SSE*), Tsallis spectral entropy

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(*TSE*), generalized escort-Tsallis spectral entropy (*GSE*) and Rényi spectral entropy (*RSE*) were then calculated. The *RSP* was used to characterize the power distribution over the frequency and to confirm the MEG slowing in AD. On the other hand, the *SSE* was used to analyze the flatness of the spectrum, while the quantifiers based on non-extensive information measures (*TSE*, *GSE* and *RSE*) were employed to explore the irregularity of the recordings, modifying the distribution of the original signal.

II. MATERIALS AND METHODS

A. Subjects and MEG recording

Twenty patients (7 men and 13 women, age = 73.05 ± 8.65 years, mean $\pm$ standard deviation SD) from the “Asociación de Familiares de Enfermos de Alzheimer” (AFAL) were included in the study. All of them fulfilled criteria for probable AD according to the clinical guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) [21]. Their cognitive function was assessed using the Mini-Mental State Examination (MMSE), obtaining a mean MMSE score of 17.85 ± 3.91 (mean $\pm$ SD). Moreover, AD patients were not taking any medication that could affect the central nervous system. Twenty-one cognitively normal volunteers (9 men and 12 women, age = 70.29 ± 7.07 years, mean $\pm$ SD) participated in the study as controls. Their mean MMSE score was of 29.10 ± 1.00 points. No significant differences were detected in the mean age of both groups ($p > 0.05$). Moreover, informed consent was obtained from all controls and all patients’ caregivers. The study was approved by the local ethics committee.

MEGs were recorded with 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”. Five minutes of spontaneous MEG activity were acquired at a sampling rate of 678.17 Hz with subjects in a relaxed state, awake and with eyes closed. A 0.1-200 Hz hardware bandpass filter and 50 Hz notch filter were also used. Subsequently, each signal was downsampled by a factor of four to reduce the data length. Artifact-free epochs of length 10 s (26.4 ± 5.5 artifact-free epochs per channel and subject, mean $\pm$ SD) were selected for further analysis. Prior to spectral analysis, each segment of 1696 samples was digitally bandpass-filtered with cut-off frequencies at 0.4 and 70 Hz.

B. Definition of the spectral entropies

The PSD for each MEG segment was calculated from the FT of the autocorrelation function. PSDs were averaged for each channel and subject to compute the mean power spectrum. Then, the *RSP* was calculated in the classical frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta1 (13-19 Hz), beta2 (19-30 Hz) and gamma (30-64 Hz). If we denote the power at each frequency band as P_j , $j = \{\text{delta, theta, alpha, beta1, beta2, gamma}\}$, then, the *RSP*

can be represented as a probability distribution,

$$p_j = \frac{P_j}{\sum_j P_j}. \quad (1)$$

Hence, four entropies (*SSE*, *TSE*, *GSE* and *RSE*) were computed from *RSP*. The *SSE* is a disorder quantifier, which has been previously employed to characterize MEG irregularity in AD [10]. It is a measure of the flatness of the spectrum, and its definition is based on the Shannon’s entropy [22],

$$SSE = -\sum_j p_j \cdot \ln[p_j]. \quad (2)$$

The *TSE* is a generalized information measure, which generalizes the notion of the *SSE*. As it is a non-logarithmic entropy, it is useful to explore the properties of a probability distribution from a new mathematical framework in relation to the *SSE*. The *TSE* is controlled by a parameter $q \in \mathbb{R}$, which can be considered as measuring the degree of non-extensivity [23]. Hence, it is possible to obtain the Boltzmann-Gibbs entropy from *TSE* in the limit $q \rightarrow 1$. Its definition is given by [20],

$$TSE(q) = \frac{1}{q-1} \sum_j [p_j - (p_j)^q]. \quad (3)$$

Regarding to the *GSE*, it is an entropy closely related to the *TSE*. Nevertheless, the probability distribution of the original signal is modified to achieve an escort distribution, providing a different framework to analyze the properties of the original signal [24]. Similarly to the *TSE*, the *GSE* is also stated by an index $q \in \mathbb{R}$, which can be identified with the parameter q , previously defined for the *TSE*. Different values of q generate escort distributions of different degree, which can be useful to analyze the mathematical structure of the original distribution. The *GSE* definition reads [20],

$$GSE(q) = \frac{1}{q-1} \left\{ 1 - \left[\sum_j (p_j)^{1/q} \right]^{-q} \right\}. \quad (4)$$

Finally, the *RSE* is also a non-extensivity generalized information measure, which can be reduced to the Boltzmann-Gibbs entropy in the limit $q \rightarrow 1$ [25]. This parameter can be used to quantify the uncertainty of a signal, and its definition is given by,

$$RSE(q) = \frac{1}{1-q} \ln \left[\sum_j (p_j)^q \right]. \quad (5)$$

It should be noticed that in order to obtain a single value per parameter and subject, and to achieve a straightforward interpretation of the results, in this first approach to the problem the measures were averaged for all channels.

All calculations were carried out with the software package Matlab (version 7.0; Mathworks, Natick, MA).

C. Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normal distribution of the variables. After the descriptive analysis, neither several variables nor their log-transformed values met parametric test assumptions. Therefore, non-parametric two-tailed Mann-Whitney U test ($\alpha = 0.05$) was used to evaluate statistical significance. In addition, binary logistic regression was employed to investigate group classification. Statistical analyses were performed using SPSS software (version 14.0; SPSS Inc, Chicago, Ill).

III. RESULTS AND DISCUSSION

We computed the PSD of the 10 s segments in the 148 channels. Results were averaged for each channel and each subject. The measures (RSP , SSE , TSE , GSE and RSE) were then computed for each averaged PSD. In order to explore the dependence of the TSE , GSE and RSE on the non-extensive parameter q , it was modified ($q = \{1.25, 1.5, 1.75, 2\}$) according to previous studies which analyzed EEG recordings using analogous quantifiers [19], [20]. Finally, mean values for all channels were computed to obtain a quantitative measure per subject. Statistical significance of each parameter was assessed using Mann-Whitney U tests, whereas classification performance was evaluated by means of binary logistic regression.

Table I summarizes both the mean values of the parameters for each group and the results of statistical and classification analyses. As it can be seen, AD patients exhibit significantly larger RSP values at the delta and theta bands than controls. However, RSP values were significantly lower in AD patients than in healthy subjects at the beta and gamma bands. This issue implies a slowing of the spontaneous MEG activity in AD, which has been previously reported in similar studies [6]–[11]. Regarding to the spectral entropies, their values indicate a statistically significant decrease in AD patients' MEGs by comparison with healthy subjects. This result suggests an irregularity decrease, in terms of the flatness of the power spectrum, for AD patients. In this sense, previous works obtained similar results, reporting an overall decrease both in irregularity [10] and complexity [12] of MEG activity in AD.

Further inspection of Table I shows that the most significant differences ($p < 0.0001$) were achieved by RSP at the delta and beta bands, with an accuracy between 80.5% and 85.4%. This issue was also reported by Fernández *et al.*, which performed an exhaustive analysis of the RSP distribution in AD patients' MEGs [8]. With regard to the spectral entropies, the statistical differences achieved with both the $RSE(\{1.25, 1.5, 1.75, 2\})$ and the $TSE(1.25)$ were close to those obtained by the RSP at the delta and beta bands. In addition, similar classification results were also obtained by the previous quantifiers, showing an accuracy between 82.9% and 85.4%. Finally, slightly greater p -values than with the previous measures ($p < 0.0005$) were obtained with the $TSE(\{1.5, 1.75, 2\})$, SSE and

$GSE(\{1.25, 1.5, 1.75, 2\})$, with a maximum accuracy of 82.9%. A similar result was obtained in a previous study ($p = 0.00023$; 82.93% accuracy), where the SSE (among other spectral measures) was used to characterize the PSD of MEGs in AD [10].

On the other hand, the analysis of the entropy dependence on the non-extensive parameter q , reveals that as q decreases, the TSE , GSE and RSE values approach to those provided by the SSE . Although previous studies have reported that the “background EEG-detection-power” decreases as the parameter q ($q > 1$) increases [17], our results indicate that this issue depends on the quantifier. Hence, the statistical differences observed in the TSE and GSE seem to decrease as q increases, whereas an opposite behavior is obtained when the RSE is analyzed. In addition, previous studies also observed that quantifiers based on Tsallis and Rényi entropies exhibited a moderate or low dependence with the parameter q [18], [20], whereas measures based on the generalized escort-Tsallis statistics showed a strong dependence on q [20]. In our analyses, a slightly dependence on q can also be observed, since both the statistical and classification results varied depending on this index. Nevertheless, further works should be carried out to accurately assess the influence of the non-extensive parameter q on the TSE , GSE and RSE .

In relation to the limitations of the study, it should be mentioned that we have used a small sample size. In this sense, it should also be appropriate to increase the number of subjects enrolled in the work, as well as to extend the analysis to other neurodegenerative disorders with similar alterations to those observed in AD. Finally, as a first approach to the problem we have averaged the whole MEG activity in the head. This issue implies a loss of spatial information and, therefore, further studies should analyze the entropic patterns in each brain region to extend our results.

IV. CONCLUSIONS

This preliminary study was performed to analyze the spontaneous MEG activity in AD patients and controls by means of several spectral measures. Both a MEG slowing and a loss in irregularity were found using the RSP and the entropic quantifiers, respectively.

Our results suggest that the spectral parameters based on extensive (SSE) and non-extensive (TSE , GSE and RSE) informational spectral tools could be useful to characterize the spontaneous MEG activity in AD, leading to a better understanding of the underlying brain dynamics. In this sense, variations of the non-extensive parameter q provide different entropy definitions. They can be used to yield new information about MEG rhythms in AD in comparison with that obtained using conventional spectral methods.

Further works should be performed to accurately explore the influence of the index q and to obtain a detailed spatial analysis.

TABLE I

MEAN VALUES FOR EACH GROUP (MEAN $\pm$ STANDARD DEVIATION, SD) AND RESULTS OF STATISTICAL AND CLASSIFICATION ANALYSES

Parameter	Controls	AD patients	p-values	Sensitivity	Specificity	Accuracy
RSP(delta)	0.20 $\pm$ 0.07	0.38 $\pm$ 0.15	0.00004	14/20 (70.0%)	21/21 (100.0%)	35/41 (85.4%)
RSP(theta)	0.14 $\pm$ 0.07	0.20 $\pm$ 0.10	0.03935	10/20 (50.0%)	18/21 (85.7%)	28/41 (68.3%)
RSP(alpha)	0.20 $\pm$ 0.08	0.17 $\pm$ 0.08	N.S.	14/20 (70.0%)	12/21 (57.1%)	26/41 (63.4%)
RSP(beta1)	0.17 $\pm$ 0.04	0.10 $\pm$ 0.05	0.00005	16/20 (80.0%)	19/21 (90.5%)	35/41 (85.4%)
RSP(beta2)	0.19 $\pm$ 0.08	0.10 $\pm$ 0.05	0.00008	18/20 (90.0%)	15/21 (71.4%)	33/41 (80.5%)
RSP(gamma)	0.09 $\pm$ 0.04	0.06 $\pm$ 0.03	0.01891	13/20 (65.0%)	14/21 (66.7%)	27/41 (65.9%)
SSE	1.66 $\pm$ 0.07	1.46 $\pm$ 0.21	0.00013	15/20 (75.0%)	19/21 (90.5%)	34/41 (82.9%)
TSE(1.25)	1.34 $\pm$ 0.05	1.18 $\pm$ 0.17	0.00009	15/20 (75.0%)	20/21 (95.2%)	35/41 (85.4%)
TSE(1.5)	1.10 $\pm$ 0.04	0.97 $\pm$ 0.14	0.00010	15/20 (75.0%)	19/21 (90.5%)	34/41 (82.9%)
TSE(1.75)	0.92 $\pm$ 0.03	0.82 $\pm$ 0.11	0.00011	15/20 (75.0%)	19/21 (90.5%)	34/41 (82.9%)
TSE(2)	0.79 $\pm$ 0.03	0.70 $\pm$ 0.09	0.00011	15/20 (75.0%)	19/21 (90.5%)	34/41 (82.9%)
GSE(1.25)	1.37 $\pm$ 0.04	1.26 $\pm$ 0.13	0.00019	15/20 (75.0%)	19/21 (90.5%)	34/41 (82.9%)
GSE(1.5)	1.14 $\pm$ 0.02	1.08 $\pm$ 0.09	0.00019	14/20 (70.0%)	19/21 (90.5%)	33/41 (80.5%)
GSE(1.75)	0.96 $\pm$ 0.01	0.92 $\pm$ 0.05	0.00017	14/20 (70.0%)	19/21 (90.5%)	33/41 (80.5%)
GSE(2)	0.82 $\pm$ 0.01	0.80 $\pm$ 0.03	0.00017	14/20 (70.0%)	19/21 (90.5%)	33/41 (80.5%)
RSE(1.25)	1.63 $\pm$ 0.08	1.41 $\pm$ 0.23	0.00009	14/20 (70.0%)	20/21 (95.2%)	34/41 (82.9%)
RSE(1.5)	1.60 $\pm$ 0.09	1.36 $\pm$ 0.25	0.00008	16/20 (80.0%)	19/21 (90.5%)	35/41 (85.4%)
RSE(1.75)	1.58 $\pm$ 0.10	1.32 $\pm$ 0.26	0.00008	16/20 (80.0%)	19/21 (90.5%)	35/41 (85.4%)
RSE(2)	1.56 $\pm$ 0.11	1.28 $\pm$ 0.26	0.00007	16/20 (80.0%)	19/21 (90.5%)	35/41 (85.4%)

N.S. = not significant

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