32nd Annual International Conference of the IEEE EMBS
Buenos Aires, Argentina, August 31 - September 4, 2010

Analysis of Spontaneous MEG Activity in Mild Cognitive Impairment Using Spectral Entropies and Disequilibrium Measures

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Abstract— **The aim of this study was to explore the ability of several spectral entropies and disequilibrium measures to discriminate between spontaneous magnetoencephalographic (MEG) oscillations from 18 mild cognitive impairment (MCI) patients and 24 controls. The Shannon spectral entropy (*SSE*), Tsallis spectral entropy (*TSE*), and Rényi spectral entropy (*RSE*) were calculated from the normalized power spectral density to evaluate the irregularity patterns. In addition, the Euclidean (*ED*) and Wootters (*WD*) distances were computed as disequilibrium measures. Results revealed statistically significant lower *SSE* and *TSE*(2) values for MCI patients than for controls ($p < 0.05$) in the right lateral region of the brain. *ED* also obtained statistically significant lower values for MCI patients than for controls using the ($p < 0.05$) in the right lateral region of the brain. These findings suggest that MCI is associated with a significant decrease in irregularity of MEG activity. In addition, the highest accuracy of 64.3% was achieved by the *SSE*. We conclude that measures from information theory can be useful to both characterize abnormal brain dynamics and help in MCI detection.**

I. Introduction

Mild cognitive impairment (MCI) is a disorder of the brain, which is considered an intermediate clinical stage between the cognitive decline of normal aging and the more serious problems caused by Alzheimer's disease (AD) [1]. Although MCI can affect multiple brain areas, such as those involved in though and action, the most common variety of MCI causes memory problems. Thus, MCI represents a subtle but measurable memory disorder, in which patients experience memory problems greater than normally expected with aging, but do not show other symptoms of dementia, such as impaired judgment or reasoning [2].

Likewise AD, MCI is a heterogeneous disease, where several subtypes can be distinguished [3]. Due to this fact, it is complex to determine whether a potential MCI patient is exhibiting cognitive changes of normal aging or the earliest stages of dementia [1]. Nowadays, there is not an effective test to detect MCI. It is diagnosed by excluding other conditions that might be causing the signs and symptoms. An exhaustive examination is carried out, including a physical exam, a neurological test, a mental status exam, laboratory tests and brain scans [3].

Despite the difficulties to achieve a diagnosis, an early and accurate identification of MCI should be attempted. A previous diagnosis of MCI is considered an important risk factor for the development of AD. Most patients with MCI develop a progressive decline in their thinking abilities over time, and AD is usually the underlying cause [4]. On the other hand, an early diagnosis is important in the case of pharmacologic interventions. Though there is no cure for MCI, current treatments may help to reduce cognitive problems. Moreover, nonpharmacologic strategies could be applied since the appearance of the first symptoms. As a conclusion, new tools are needed to help in MCI detection [2].

Given the fact that MCI affects the brain cortex, electroencephalographic (EEG) and magnetoencephalographic (MEG) signals can reflect anatomical and functional deficits of the brain. EEG and MEG recordings are related [5]. However, scalp EEG is much more affected by the conductivities of the skull and the scalp than MEG [6]. Due to this fact, it can be hypothesized that MEG might provide a more accurate vision of the cortical activity function than scalp EEG [7].

The alterations that MCI produces in electromagnetic brain oscillations have been analyzed by means of EEG [8]–[10], whereas only a few studies have focused on MEG [11]. In this sense, several differences have been found in the MEG activity between MCI and AD patients. MEG studies have shown increased slow rhythms and reduced fast activity in AD compared to MCI, using median frequency and alpha frequency [12], [13]. Some authors have also reported an increase of complexity in MCI patients' MEG background activity using non-linear measures [14]. In addition, studies analyzing functional connectivity have found different patterns of coherence and synchronization likelihood [15]. Nevertheless, only subtle differences have been observed between MCI patients and elderly healthy subjects [13]–15].

This study is a first approach to explore the ability of several measures from information theory to characterize MEG rhythms in MCI. The proposed measures are based on the Fourier transform (FT). Firstly, the FT was used to compute the power spectral density (*PSD*) for each MEG recording in five brain regions. Shannon spectral entropy

Manuscript received March 30, 2010. This work was supported in part by the project TEC2008-02241 from "Ministerio de Ciencia e Innovación". *Asterisk indicates corresponding author*.

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(*SSE*), Tsallis spectral entropy (*TSE*), and Rényi spectral entropy (*RSE*) were then calculated to explore the irregularity patterns in terms of the flatness of the spectrum. In addition, the Euclidean (*ED*) and the Wootters (*WD*) distances were employed to provide an alternative way to quantify the irregularity of MEGs by means of disequilibrium measures.

II. Materials and Methods

A. Subjects and MEG Recording

Eighteen patients (8 men and 10 women, age = 75.4 ± 5.5 years, mean ± standard deviation SD) from the "Asociación de Familiares de Enfermos de Alzheimer" and twenty-four cognitively normal volunteers (9 men and 15 women, age = 71.7 ± 6.5 years, mean ± SD) participated in the study. All patients were diagnosed following Petersen's criteria [16]. Their cognitive function was evaluated using the Mini-Mental State Examination (MMSE). MCI patients obtained a mean MMSE score of 25.7 ± 1.8 (mean ± SD), whereas controls had a mean MMSE score of 28.9 ± 1.2 points. No significant differences were observed in the mean age of both groups ($p > 0.05$, Mann-Whitney U test). MCI patients and controls were not taking any medication that could affect the central nervous system. Informed consent was obtained from all controls and patients' caregivers. The study was approved by the local ethics committee.

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. MEGs 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 band-pass filter and a 50 Hz notch filter were applied. Each recording was processed with a low-pass filter before downsampling by a factor of 4 to reduce the data length. Artifact-free epochs of length 10 s (28.4 ± 3.6 artifact-free epochs per channel and subject, mean ± SD) were selected for further analysis. In addition, outer sensors were excluded from the analysis due to the low signal-to-noise ratio. Prior to time-frequency analysis, each MEG signal of 1696 samples was digitally band-pass filtered between 1 and 70 Hz.

B. Definition of Spectral Parameters

The MEG irregularity can be indirectly analyzed applying several measures to their power-frequency distributions [17]. In the present work, five spectral parameters based on the FT were calculated to quantify the irregularity of the signal: *SSE, TSE, RSE*, *ED* and *WD*. MEG recordings were filtered between the cut-off frequencies, f_1 = 1 Hz and f_2 = 70 Hz, and segmented. Each segment contained 10 s of non-overlapping data (1696 samples). The *PSD* for each MEG segment was calculated as the FT of the autocorrelation function. *PSD*s were averaged to obtain the mean power spectrum in five brain regions. Finally, the *PSD* was normalized to scale from 0 to 1 to obtain the normalized *PSD* (PSD_n),

$$PSD_n(f) = \frac{PSD(f)}{\sum_{f=f_1}^{f_2} PSD(f)} \tag{1}$$

Three entropies were calculated from the PSD_n, which was considered as a probability distribution. The *SSE* is a disorder quantifier, which has been previously employed to characterize MEG irregularity in AD [17], [18]. Its definition is based on the Shannon's entropy and quantifies the flatness of the power spectrum [19].

$$SSE = -\sum_{f=f_1}^{f_2} PSD_n(f) \cdot \ln[PSD_n(f)] \tag{2}$$

The *TSE* is a generalized information measure, which extends the notion of the *SSE*. It is a non-logarithmic entropy, what makes it useful to explore the properties from a new mathematical framework. The *TSE* is controlled by the entropic index, $q \in \Re$, which can be considered as a measure of the degree of non-extensivity [20]. Hence, it is possible to obtain the *SSE* from the *TSE* in the limit $q \to 1$. Its definition is given by,

$$TSE(q) = \frac{1}{q-1} \sum_{f=f_1}^{f_2} \left\{ PSD_n(f) - [PSD_n(f)]^q \right\} \tag{3}$$

The *RSE* is an extensive generalized information measure, which can be reduced to the *SSE* entropy in the limit $q \to 1$ [21]. This measure can be used to quantify the uncertainty of a signal, and its definition is given by,

$$RSE(q) = \frac{1}{1-q} \ln \left[\sum_{f=f_1}^{f_2} [PSD_n(f)]^q \right] \tag{4}$$

In addition to the entropies, two disequilibrium measures were calculated as estimators of the irregularity in a signal. The original measure of disequilibrium is the *ED*, which is defined as the distance in the probability space between the considered distribution and the uniform distribution [22]. It can be then considered as a measure of irregularity, and it is defined as follows,

$$ED = \sum_{f=f_1}^{f_2} [PSD_n(f) - 1/N]^2 \tag{5}$$

Another definition of disequilibrium is the *WD*. It provides an alternative framework to quantify the distance between distributions [23]. Its definition is given by,

$$WD = \cos^{-1} \left\{ \sum_{f=f_1}^{f_2} \sqrt{PSD_n(f)} \cdot \sqrt{1/N} \right\} \tag{6}$$

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, while homocedasticity was evaluated with Levene test. After the descriptive analysis, we found that the log-transformed values met parametric test assumptions. Therefore, two-way ANOVAs (with group as between-subject factor and brain region as within-subject factor) with contrast were performed to explore statistical significance for each parameter ($\alpha = 0.05$) at five brain regions (anterior, central, left lateral, posterior, and right lateral).

Receiver operating characteristics (ROC) curves with a leave-one-out cross-validation (LOO-CV) procedure were used to visually evaluate the ability of each parameter to distinguish between MCI patients and controls. In order to quantify the parameter's performance, we used the area under ROC curve (AUC) and the accuracy obtained with the optimum threshold.

All statistical analyses were performed using SPSS software (version 15.0; SPSS Inc, Chicago, IL).

III. Results and Discussion

The PSD_n of the 10 s epochs was computed for each channel. Results were averaged over five brain regions for each subject (anterior, central, left lateral, posterior, and right lateral), which were defined according to previous works [14], [17]. Spectral entropies and disequilibrium measures were then computed. In the case of *TSE* and *RSE* the entropic index was set to 2 and 3.5 respectively, according to the optimal values obtained in a previous research [17].

Table I summarizes the mean values and the standard deviations of the parameters for each group that obtained significant *p*-values, together with the results of the statistical analysis. MCI patients obtained significantly lower *SSE* and *TSE*(2) values ($p < 0.05$) than controls in the right lateral region, which suggests a significant decrease in the irregularity of MCI patients' MEGs. On the other hand, MCI patients exhibited significantly higher *ED* values ($p < 0.05$) than controls in the right lateral region. This issue indicates that MEG recordings from MCI patients have a PSD_n more different to the equiprobable distribution than healthy controls, which suggest a decrease in irregularity again. The results are in agreement with the decrease in irregularity reported in previous studies which analyzed spontaneous MEG activity in AD using spectral entropies [17], [18] and non-linear parameters [24], [25]. Nevertheless, to the best of our knowledge this is the first work addressing the characterization of the irregularity patterns in MCI. Related to the previous issue, Fernández *et al*. [14] observed a trend to decrease in non-linear complexity of MCI patients, though they did not obtained significant differences.

Fig. 1 depicts the ROC curves for the significant parameters, previously presented in Table I. A summary of their characteristics can be observed in Table II, where accuracy and AUC applying LOO-CV are shown. The *SSE* achieved both the highest AUC of 0.664 ± 0.014 and accuracy of 64.3%. It is noteworthy that previous studies have suggested the usefulness of *SSE* to discriminate between AD patients and controls using MEG recordings [17], [18], [24]. The *TSE*(2) and the *ED* obtained slightly lower classification statistics than the *SSE*, with an AUC of 0.655 ± 0.014 and an accuracy of 61.9%. Studies analyzing functional connectivity and lentification of the oscillatory cerebral activity in MCI and elderly healthy subjects obtained similar AUC and accuracy statistics [15]. Nevertheless, they did not apply a LOO-CV procedure. In addition, an advantage of the methods used in the present study, compared to previous efforts, is their ability to carry out a analysis of the underlying dynamics, at the same time an easily interpretation of the results can be achieved. Therefore, it is possible to obtain an alternative description of the brain dynamics in MCI to conventional spectral and non-linear methods.

TABLE I
Average Values (Mean ± SD) for Significant Parameters in Both Groups and the Results of the Statistical Analysis

Parameter	Region	Controls	MCI patients	*p*-value
SSE	Right Lateral	0.8750 ± 0.0253	0.8566 ± 0.0281	0.0292
TSE(2)	Right Lateral	0.9985 ± 0.0005	0.9979 ± 0.0010	0.0230
ED	Right Lateral	0.0015 ± 0.0005	0.0021 ± 0.0010	0.0230

Finally, some limitations should be addressed in future works. We used a small sample size. Likewise, the number of subjects enrolled in the study should be increased. The analysis should also be extended to other neurodegenerative disorders with similar alterations to those observed in MCI and AD. In addition, as a first approach to the problem, we set the entropic values for *TSE* and *RSE* taking into account the results obtained in a previous study, where AD patients and controls were compared. Further works should be performed to accurately explore the influence of the index *q* in MCI.

IV. Conclusion

This preliminary study was performed to analyze the spontaneous MEG activity in MCI patients and controls by means of three spectral entropies (*SSE, TSE,* and *RSE*), and two disequilibrium measures (*ED* and *WD*). A significant loss in irregularity was found in MCI patients' MEGs. Furthermore, our results suggest that the entropies and the disequilibrium measures based on *PSD* could be useful to both characterize the abnormal brain dynamics associated with MCI and help in diagnosis. The measures from information theory can be used to yield new information about MEG rhythms in MCI in comparison with that obtained using conventional spectral and non-linear methods.

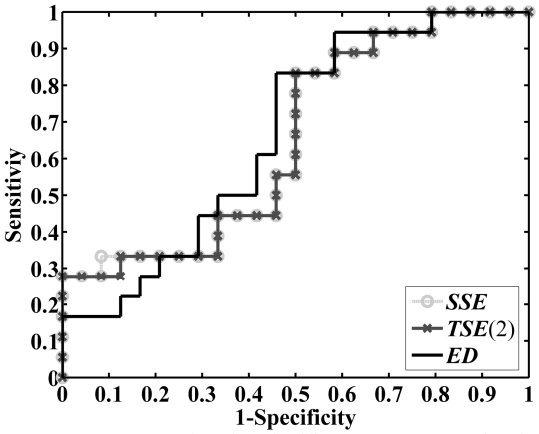

Fig. 1. ROC curves for the significant parameters showing the discrimination between MCI patients and controls.

TABLE II
ACCURACY AND AUC (MEAN ± SD) OF THE ROC ANALYSIS WITH A LOO-CV PROCEDURE USING THE SIGNIFICANT PARAMETERS

Parameter	Region	Accuracy (%)	AUC
SSE	Right Lateral	64.3	0.664 ± 0.014
TSE(2)	Right Lateral	61.9	0.655 ± 0.014
ED	Right Lateral	61.9	0.655 ± 0.014

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