Analysis of Spontaneous MEG Activity in Mild Cognitive Impairment and Alzheimer's Disease using Jensen's Divergence

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Abstract— **The aim of this study was to analyze the changes that mild cognitive impairment (MCI) and Alzheimer's disease (AD) elicit in brain dynamics. For this task, the spontaneous magnetoencephalographic (MEG) activity from 36 AD patients, 18 MCI subjects and 24 healthy controls was analyzed. A disequilibrium measure, Jensen's divergence, was used to estimate the irregularity of neural dynamics. Results revealed that AD patients displayed significant changes (p<0.05) in the patterns of irregularity in comparison with MCI subjects and healthy controls. Slight differences between MCI subjects and elderly controls were also found. Our results suggest that AD progression is accompanied by region-specific patterns of abnormalities in the neural activity.**

I. NTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of dementia [1]. Different brain regions become progressively involved during the course of the disease. As a consequence, neural activity is modified [2]. Considerable effort has been devoted to understanding the underlying brain dynamics. In this regard, the characterization of its prodromal form (i.e. mild cognitive impairment, MCI) is crucial to gain further insights into the early alterations that lead to AD [3].

Noninvasive neurophysiological techniques, like electroencephalography (EEG) and magnetoencephalography (MEG) have been widely used in studies aimed at increasing the understanding of the dynamical processes of complex brain systems [2]. EEG and MEG are related, though they reflect different properties of neural activity. Thereby, MEG might be more sensitive when recording the ongoing neural oscillations than scalp EEG [4].

Several studies have addressed the characterization of neural dynamics in AD [4], [5]. Accumulating evidence supports the notion that AD is associated with a progressive slowing of brain oscillatory activity [6], a loss of irregularity [7]–[9] and complexity [10], [11], and diverse abnormalities in the connectivity and synchronization patterns [12], [13]. Nevertheless, only a few studies focused on analyzing resting-state neural activity in early stages of AD. In this regard, intermediate abnormalities between those observed in normal aging and AD have been reported in MCI [6], [9], [11]. Certainly, more research is required to establish a consistent characterization of neural dysfunction in MCI.

It is noteworthy that measures from information theory introduce an alternative framework to analyze complex brain dynamics to that offered by linear and non-linear parameters. Previous studies have shown that they can provide promising insights to understand neural dynamics [7], [9], [11]. The present research introduces the application of a parameter from information theory: Jensen's divergence. It is a disequilibrium measure useful to characterize the irregularity of neural activity. In this study, we wanted to analyze whether the application of Jensen's divergence could be useful to account for the abnormalities that MCI and AD elicit in brain dynamics.

II. MATERIALS AND METHODS

A. Subjects and MEG Recordings

Seventy-eight subjects were selected to participate in the study. Socio-demographic and clinical data are summarized in Table I. Specifically, 36 patients with probable AD were recruited from the 'Asociación de Familiares de Enfermos de Alzheimer (AFAL)' and the Geriatric Unit of the 'Hospital Clínico Universitario San Carlos' (Madrid, Spain). Diagnoses were made according to the clinical guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association [14]. Eighteen MCI subjects from AFAL were also included in the study. Diagnoses of MCI were based on Petersen's criteria [15]. Finally, 24 volunteers were enrolled in the study as control group. Elderly controls were cognitively healthy subjects with no history of neurological or psychiatric disorders. It is noteworthy that nonsignificant differences were found in the mean ages or genders of controls, MCI subjects, and AD patients (p > 0.05, Kruskal-Wallis test). Neither MCI subjects nor AD patients were taking any medication that could affect MEG recordings at the time of study.

All participants (or patient's caregivers if required) gave their informed consent to participate in the study. The local Ethics Committee approved the study protocol.

B. MEG Recordings

Five minutes of spontaneous brain activity were recorded from the 78 participants using a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging).

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TABLE I. SOCIO-DEMOGRAPHIC AND CLINICAL DATA OF THE COHORT OF SUBJECTS ENROLLED IN THE STUDY

Data[a]	Group		
	Controls	*MCI subjects*	*AD patients*
N	24	18	36
Age (years)	71.7 ± 6.5	74.9 ± 5.6	74.1 ± 6.9
Gender (M:F)	9:15	8:10	12:24
MMSE[b]	28.9 ± 1.2	25.7 ± 1.8	18.1 ± 3.4
FAST[c]	1.7 ± 0.5	3.0 ± 0.0	4.2 ± 0.4

a. Values are given as: mean ± standard deviation

b. MMSE: Mini-mental State Examination

c. FAST: Functional Assessment Staging

MEG equipment was placed in a magnetically shielded room in the 'Centro de Magnetoencefalografía Dr. Pérez-Modrego' of the Complutense University of Madrid (Spain). Subjects were asked to remain relaxed, awake, and with their eyes closed. The sampling frequency was 678.17 Hz. A 0.1-200 Hz hardware band-pass filter was applied. Each MEG recording was downsampled by a factor of 4 to reduce the data length. Then, MEG signals were digitally filtered using a 50 Hz notch filter and a finite impulse response (FIR) filter with Hamming window and cut-off frequencies at 1 and 65 Hz. Artifact rejection was carried out following a two-step approach. Firstly, an independent component analysis (ICA) was performed to discard components related to eyeblinks and cardiac activity. Secondly, artifact-free MEG epochs of 5 s were selected by visual inspection for further analysis. An average (± standard deviation) of 20.0±10.4 artifact-free epochs per channel and subject were finally selected.

C. Notion of Disequilibrium

A given probability distribution function (PDF) can be characterized by an information measure I. Thereby, $I[P]$ is the measure that quantifies the uncertainty associated with the physical processes described by the probability distribution $P=\{p_i, i=1,\ldots,N\}$, where N represents the number of possible states of the system under study [16]. Our knowledge of the underlying process characterized by the PDF is maximal if $I[P] = I_{min} = 0$. On the other hand, our ignorance about which of the N possible states will actually take place is maximized if $I[P] = I[P_e] = I_{max}$ ($P_e=\{1/N, i=1,\ldots,N\}$, being the uniform distribution) [16]. Indeed, I can be defined using diverse measures. A common definition of I is based on entropy. Thereby, for a discrete distribution P, we can use the canonical formulation of Shannon's logarithmic entropy [16]

$$S[P] = -\sum_{j=1}^{N} p_j \cdot \ln(p_j) \,. \quad (1)$$

In the case of the uniform distribution P_e, Shannon's entropy is given by $S[P_e]=\ln(N)$.

The previous notion of entropy lets us quantify the "information" or "disorder" of a system, though it is not enough to describe the underlying system "architecture". Therefore, information theory introduces the concept of disequilibrium. This measure quantifies the distance of the given PDF P to the PDF that represents the equilibrium P_e as follows [16]

$$Q[P] = Q_0 \cdot D[P, P_e] \,, \quad (2)$$

where $D[\cdot]$ represents the distance and Q_0 is a normalization constant ($0 \le Q \le 1$). From (2), it follows that Q takes values different from zero if there are "privileged", or "more likely" states [16].

Several metrics can be used to quantify the distance, like the Euclidean norm, the Wooter's distance, and the Hellinger distance, among others. An alternative to them is the use of divergences. Two divergences classes are usually considered: (i) divergences defined as relative entropies, like the Kullback-Leibler relative entropy; and (ii) divergences defined as entropic differences. Jensen's divergence belongs to the latter class. It is noteworthy that, in general, entropic differences do not define an information gain (and as a consequence a divergence), since they are not necessarily positive definite. In order to overcome this problem, Jensen's divergence introduces a symmetric version of the Kullback-Leibler relative entropy [16]. In this study, Jensen's divergence is expressed in terms of Shannon's entropy for $\beta = 1/2$ as [17]3

$$D_J[P_1, P_2] = S[\beta P_1 + (1-\beta)P_2] - \beta S[P_1] - (1-\beta)S[P_2] = \cdots = S\left[\frac{P_1 + P_2}{2}\right] - \frac{S[P_1]}{2} - \frac{S[P_2]}{2} \,. \quad (3)$$

Note that (3) defines a metric to quantify the dissimilarity between two PDFs, P_1 and P_2. In order to define the disequilibrium, P_1 is replaced by the given PDF P, and P_2 by the PDF that represents the equilibrium P_e. Moreover, Q_0 should be defined as [17]

$$Q_0^J = -2 \cdot \left\{ \left(\frac{N+1}{N}\right) \cdot \ln(N+1) - 2 \cdot \ln(2 \cdot N) + \ln(N) \right\}^{-1} \,. \quad (4)$$

D. Disequilibrium as an Irregularity Quantifier

Previous EEG and MEG studies showed the usefulness of the Euclidean norm, the Wooter's distance, and the Kullback-Leibler relative entropy to analyze the irregularity [11], [18] and the similarity [19] of brain activity in dementia. In the present study, Jensen's divergence was introduced to quantify the disorder of neural activity. For that task, the normalized power spectral density (PSD_n) was computed for each 5-s length MEG epoch (N = 848 samples) in the [1 65] Hz frequency range. PSD_n was calculated as the Fourier transform of the autocorrelation function. It follows that $\sum_f PSD_n(f) = 1$. Thus, we can identify PSD_n as a PDF, representing the state of our system [7], [16]. In order to compute Jensen's divergence, we used (3), replacing P_1 by PSD_n and P_2 by P_e. The result was normalized by (4), according to (2). This definition of Jensen's divergence (Q^J) can be considered as an irregularity quantifier that measures the distance between the PDF that summarizes the spectral content of MEG recordings and the uniform PDF.

E. Statistical Analysis

The statistical analysis was performed in three steps: (i) exploratory analysis; (ii) global statistical analysis; and (iii) sensor-level statistical analysis.

The exploratory analysis revealed that variables did not meet parametric test assumptions. Thus, nonparametric tests were used. Grand average Q^J values for controls, MCI subjects, and AD patients were compared using Kruskal-Wallis test ($\alpha = 0.05$). Pairwise comparisons were performed by means of Bonferroni-corrected Mann-Whitney U-tests ($\alpha = 0.05/3 = 0.0167$). Finally, sensor-level statistics were computed using a multiple comparison nonparametric permutation test [20]. This test is useful to control type I error when the multiplicity of testing must be taken into account (e.g. 148 sensors) [9].

Signal processing and statistical analyses were performed using the software packages Matlab (version 7.14 Mathworks, Natick, MA) and SPSS Statistics (version 20, IBM Corp, Armonk, NY).

III. Results

A. Global Analysis

In a first step, Q^J values were averaged over all sensors to obtain a single value per subject. Fig. 1 depicts the boxplots corresponding to the grand average Q^J values for each group. The analysis showed a significant main effect of 'group' variable ($\chi^2 = 11.0$, $p = 0.0041$). Pairwise comparisons indicated that AD patients reached statistically significant higher Q^J values than controls ($Z = -2.912$, $p = 0.0036$) and MCI subjects ($Z = -2.514$, $p = 0.0119$). Nonsignificant differences were found between MCI patients and controls ($Z = -0.292$, $p > 0.0167$).

B. Sensor-level Analysis

Analyses at the sensor level are summarized in Fig. 2, where the differences in the spatial distributions for each pair of groups can be observed. The spatial analyses showed a widespread increase of Q^J for AD patients when compared to controls, including frontal, temporal, and lower right posterior regions. Likewise, AD patients obtained an increase of Q^J in comparison to MCI subjects, which was mainly localized in left frontal and temporo-posterior regions. On the other hand, MCI subjects displayed a slight decrease of Q^J in posterior and left frontal regions, as well as a slight increase in upper right temporal region, when compared to controls.

IV. Discussion

Our findings suggest that AD can be associated with a global decrease of irregularity, whereas MCI exhibits a degree of irregularity similar to normal aging. These results are in agreement with the loss of irregularity associated with AD, which was previously reported using spectral [7], [9], [11] and nonlinear parameters [8], [10]. Our results also indicate that the spatial are significantly different in MCI and AD when compared to normal aging, though controls and MCI subjects exhibit an overlapped distribution of abnormalities. Nevertheless, some region-specific differences can be observed between MCI subjects and controls. Similar findings were reported in previous MEG studies, in which subtle MCI-characteristic patterns in neural dynamics were found [9]–[11].

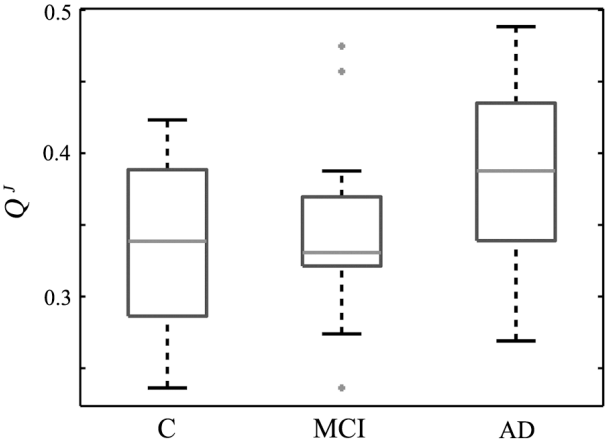

Figure 1. Boxplots for each group (C: healthy controls; MCI: MCI subjects; AD: AD patients) corresponding to the grand average Jensen's divergence values (Q^J).

Abnormalities in the distribution of Q^J involve changes of transient information flow dynamics. Accumulating evidence suggests that different neurodegenerative diseases can be related to different patterns of cognitive information flow instabilities [21]. Likewise, some studies associate changes in entropy and disequilibrium with a loss of information content [11] and a decrease in information processing [7] within the brain cortex.

Several methodological and clinical issues of the present research merit further consideration. Firstly, other disequilibria should be analyzed. Likewise, it would be interesting to analyze whether disequilibria could be useful to analyze neural couplings between different sensors. On the basis of the established coupling patterns, a complex network analysis could be performed to further understand the changes that AD and its prodromal stage (i.e. MCI) elicit in the organization of brain networks. Finally, it would be appropriate to extend our study to other forms of dementia, which may also elicit abnormalities in brain activity similar to those observed for MCI and AD (e.g. vascular dementia).

V. Conclusion

Our results support the notion that MCI and AD elicit a region-specific decrease in the irregularity patterns of brain activity in comparison with those found for elderly controls. Furthermore, measures from information theory can be useful to quantify the abnormal neural dynamics associated with dementia. Further studies will address the role of divergences to characterize brain network organization in MCI and AD.

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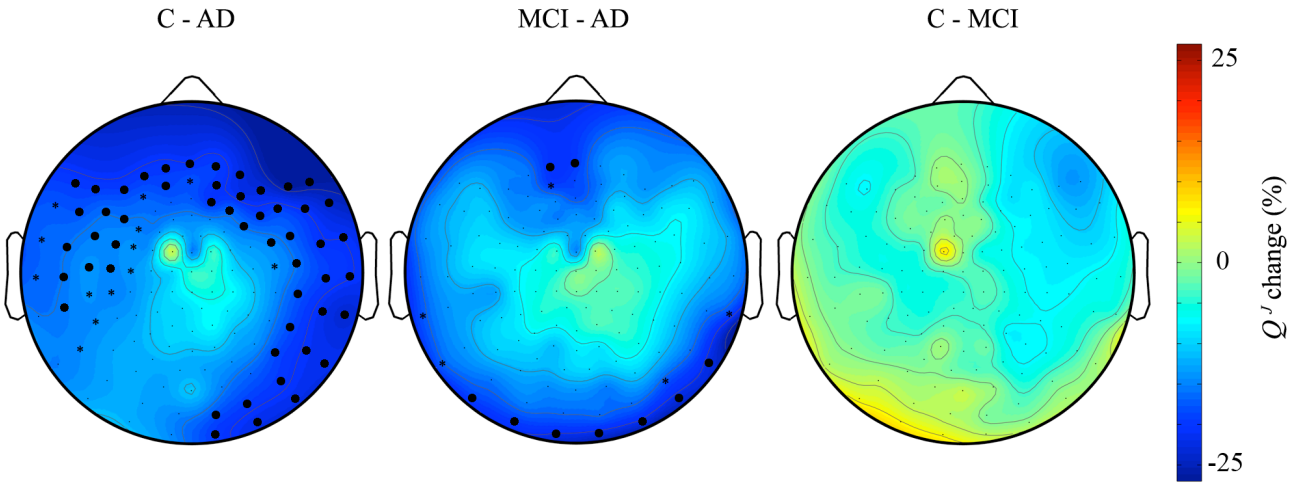

Figure 2. Sensor level topographic maps of the statistics computed for Jensen's divergence (Q^J) between controls and AD patients (C – AD), MCI subjects and AD patients (MCI – AD), and controls and MCI subjects (C – MCI). Dots (•) and asterisks (*) indicate sensors showing statistically significant differences (p<0.05, permutation test) and a trend towards significance (p<0.08, permutation test), respectively.

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