Analysis of Electroencephalographic Dynamic Functional Connectivity in Alzheimer's Disease

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Abstract

The aim of this study was to characterize the dynamic functional connectivity of resting-state electroencephalographic (EEG) activity in Alzheimer's disease (AD). The magnitude squared coherence (*MSCOH*) of 50 patients with dementia due to AD and 28 cognitively healthy controls was computed. *MSCOH* was estimated in epochs of 60 s subdivided in overlapping windows of different lengths (1, 2, 3, 5 and 10 s; 50% overlap). The effect of epoch length was tested on *MSCOH* and it was found that *MSCOH* stabilized at a window length of 3 s. We tested whether the *MSCOH* fluctuations observed reflected actual changes in functional connectivity by means of surrogate data testing, with the standard deviation of *MSCOH* chosen as the test statistic. The results showed that the variability of the measure could be due to dynamic functional connectivity. Furthermore, a significant reduction in the dynamic *MSCOH* connectivity of AD patients compared to controls was found in the delta (0–4 Hz) and beta-1 (13–30 Hz) bands. This indicated that AD patients show lesser variation in neural connectivity during resting state. Finally, a correlation between relative power and standard deviation was found, suggesting that an increase/peak in power spectrum could be a pre-requisite for dynamic functional connectivity in a specific frequency band.

Keywords

Alzheimer's disease • Dynamic functional connectivity
Electroencephalogram • Neural dynamics
Coherence • Relative power

1 Introduction

Alzheimer's disease (AD) neurodegeneration has an effect on the temporally coordinated brain networks, which underlie cognitive functions. These networks become more abnormal with the progression of AD, as alterations in the processing and transmission of information begin to appear [1]. The aberrant brain networks associated to AD can be reflected in the alterations of the synchronization patterns and brain connectivity observed in resting-state electroencephalographic (EEG) recordings [1].

The majority of studies focusing on brain synchronization and connectivity during resting state assume that functional connectivity (FC) remains temporally stationary. However, it is important to take the spontaneous fluctuations of brain activity into account, as it has been suggested that resting-state activity is not stationary [2]. Thus, the quantification of dynamic changes in FC metrics could provide relevant information regarding the stability of brain networks [3].

Most dynamic functional connectivity (dFC) studies in the literature have been performed with functional magnetic resonance imaging (fMRI) recordings [3]. Therefore, the study of dFC on electroencephalographic (EEG) recordings is of great interest. In the specific case of AD, only a small number of studies have addressed the characterization of FC variability patterns [3].

This paper presents a novel methodology, aimed at obtaining a first approximation to the dynamics of FC in AD. Specifically, this study addresses the following research questions: (i) what epoch length is needed to obtain stable connectivity measures?; (ii) can dFC be found in AD

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patients and healthy controls?; (iii) do dFC patterns differ between both groups?

2 Materials

2.1 Subjects

A population of 28 healthy control subjects (C) and 50 patients with AD was analyzed. The subjects were matched by age. Patients were diagnosed according to the criteria of the National Institute on Aging and Alzheimer's Association (NIA-AA) [4]. The controls were elderly people without cognitive impairment, or history of neurological or psychiatric diseases. None of the participants took medications that could influence EEG records.

The socio-demographic characteristics of each group are specified in Table 1. All participants and caregivers were informed about the research and study protocol and gave their written and informed consent. The Ethical Committee of the "Río Hortega" University Hospital (Valladolid, Spain) approved the study according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2 Electroencephalographic Recordings

EEG signals were recorded using a 19-channel EEG system (XLTEK®, Natus Medical) at the Department of Clinical Neurophysiology of the "Río Hortega" University Hospital. EEG activity was acquired from Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1 y O2, at a sampling frequency of 200 Hz. Subjects were asked to remain with eyes closed, awake, and still during EEG acquisition. Five minutes of EEG activity were recorded for each subject. After a preliminary independent component analysis to remove artifacted components, the EEG recordings were then preprocessed in three steps: (i) filtering using a notch filter (50 Hz) and a Hamming window bandpass filter ([1 70] Hz); (ii) segmentation into 5 s epochs; and (iii) visual rejection of artifacts, selecting the first 60 consecutive seconds without artifacts for each subject.

3 Methods

3.1 Estimation of Variability

Coherency (COH) is a measure that analyzes the consistency between the EEG activity of different pairs of electrodes in order to characterize the connectivity between brain regions. COH is the standardized cross-spectrum of signals X and Y across trials, divided by the product of their power spectrum. Magnitude squared COH (MSCOH) combines sensitivity to both phase and magnitude synchrony and is defined as [5]:

$$MSCOH_{xy}(f,t) = \left|COH_{xy}(f,t)\right|^2 = \frac{\left|S_{XY}(f,t)\right|^2}{P_X(f,t)P_y(f,t)} \quad (1)$$

where S_{XY} is the cross-spectrum of X and Y, and P_X and P_Y are the power spectral density (PSD) of X and Y, respectively. The relative power (RP) was computed from the PSD in the conventional frequency bands: delta (δ, 1–4 Hz), theta (θ, 4–8 Hz), alpha (α, 8–13 Hz), beta-1 (β1, 13–19 Hz), beta-2 (β2, 19–30 Hz) and gamma (γ, 30–70 Hz).

3.2 Protocol

In order to study the dynamic properties of functional connectivity coupling patterns, MSCOH was computed between each pair of electrodes over the 60 s epochs by means of sliding windows with 50% overlap. Afterwards, the mean value of MSCOH (μ_{MSCOH}) and the standard deviation (κ_{MSCOH}) were obtained. κ_{MSCOH} was used as the test statistic in order to detect the existence of dFC [6]. The connectivity matrixes for each frequency band were grouped into five regions (frontal, left-temporal, right-temporal, central and parieto-occipital) and inter-regional and intra-regional μ_{MSCOH} and κ_{MSCOH} values were averaged among the electrodes within each region pair. After this procedure, the connectivity matrix was reduced to a 5×5 size (5 regions). All subsequent analyses were performed on these matrixes. This procedure was performed on windows of 1, 2, 3, 5 and 10 s, in the aforementioned 6 conventional frequency bands.

Table 1 Socio-demographic and clinical data. Mean values ± standard deviation. A: primary education or below; B: secondary education or above; MMSE: Mini-Mental State Examination

Data	Alzheimer's disease	Controls
Number of subjects	50	28
Age (years)	79.9 ± 5.8	76.1 ± 34.0
Gender (male:female)	21:28	8:20
Education level (A:B)	37:13	9:19
MMSE	21.2 ± 4.0	28.9 ± 1.1

3.3 Statistical Analysis

Shapiro-Wilk and Levene tests showed that μ_{MSCOH} and κ_{MSCOH} values did not meet parametric test conditions. Then, the Mann-Whitney *U*-test was used to evaluate the differences between groups across each frequency band and region. An FDR correction was performed in order to correct for multiple comparisons. Furthermore, a Spearman correlation analysis was performed between the RP values and the average κ_{MSCOH} values of each channel.

3.4 Analysis of Window Stability

The Friedman test was used on the μ_{MSCOH} values to detect the effects of window length on the MSCOH measures. In case the Friedman test showed a significant effect, Dunn's multiple comparison test was applied to determine the window in which the MSCOH measurements became stable, defined as the shortest window length that does not show significant differences with longer window sizes [7].

3.5 Detection of Dynamic Functional Connectivity

It is important to take into account the fact that the mere presence of fluctuations in connectivity measures is not sufficient proof of the existence of dFC. Due to the noisy nature of the recordings, the fact that the observed connectivity values are estimates of the true FC values cannot be ignored [6]. Therefore, in order to determine whether the observed fluctuations reflect real FC changes, an adequate statistical test must be carried out [6]. We followed the statistical test described by Prichard and Theiler [8], which has been previously used by Hindriks et al. [6]. In our case, 1000 surrogate versions of each EEG segment were constructed from the original signals.

4 Results and Discussion

First, we determined the window size in which the MSCOH measurements became stable. It was found that for both groups this size was 3 s. All further tests were thus performed on values obtained with a 3 s sliding window. We then assessed whether the κ_{MSCOH} values were statistically significant [6]. For each, inter-regional and intra-regional pair we performed an FDR correction on the *p*-values associated with the *z*-scores of all the connections within each pair. After this, we determined that a regional pair had dFC if at least one of the connections within it had a statistically significant κ_{MSCOH} value after the FDR correction.

Figure 1a shows the number of subjects that showed statistically significant μ_{MSCOH} in each regional pair. The beta-1 band showed the highest number of regional pairs

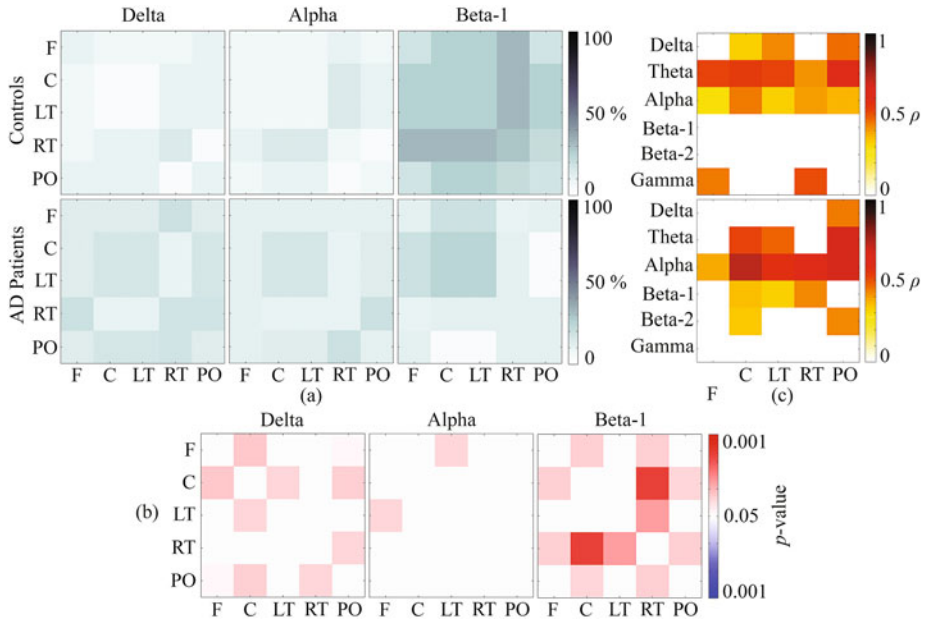

Fig. 1 MSCOH dFC analysis for a 3-s sliding window. **a** Percentage of subjects that showed statistically significant μ_{MSCOH} in each regional pair for each group. **b** Statistically significant *p*-values for the κ_{MSCOH} comparisons between groups. Red values indicate greater κ_{MSCOH} for C than AD patients, while blue values indicate greater κ_{MSCOH} for AD patients than C. **c** Correlation between RP values and κ_{MSCOH} for each group. Only the bands with significant between-group differences are shown. Correspondence with regions F: frontal, C: central, LT: left-temporal, RT: right-temporal, PO: parieto-occipital (Color figure online)

with dFC, especially for controls, nearing 50% of subjects in some cases. The statistical differences in μ_{MSCOH} between groups are also shown in Fig. 1b. The most statistically significant differences were located in the beta-1 band, especially in the connections between the right-temporal region and the remaining ones. These results are consistent with previous findings that support the role of the right hemisphere in brain disconnection related to AD [9]. Less statistically significant differences were also found in the delta band. Controls showed more variation in connectivity than AD patients, which is in agreement with other studies that found a loss of irregularity and variability in AD neural activity [9].

The correlation analysis between RP and the average κ_{MSCOH} values of each EEG channel in each band, displayed in Fig. 1c, showed statistically significant positive correlation in the delta, theta and alpha band for most regions in controls. AD patients, on the other hand, showed weaker positive correlation in the beta-1 band as well, suggesting that spectral power is a pre-requisite for dFC.

This study has some limitations. Firstly, more controls should be included in the database in order to balance the number of AD patients and controls. Furthermore, a third group of mild cognitive impairment (MCI) patients should be included in future studies, given its importance as a prodromal form of AD [9].

5 Conclusion

The results suggest that MSCOH variability could be due to dFC. Moreover, AD patients show lesser variation in neural connectivity than controls, which suggests a loss of variability in AD. Finally, the correlation between relative power and κ_{MSCOH} hints that a peak in power spectrum in a frequency band could be a pre-requisite for dFC.

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Conflict of Interest There are no conflicts of interest that could influence this research work.

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