Phase-Amplitude Coupling Analysis of Spontaneous EEG Activity in Alzheimer's Disease

Jesús Poza-*IEEE Senior Member*, Alejandro Bachiller-*IEEE Student Member*, Carlos Gómez-*IEEE Senior Member*, María García-*IEEE Senior Member*, Pablo Núñez, Javier Gomez-Pilar-*IEEE Student Member*, Miguel A. Tola-Arribas, Mónica Cano, and Roberto Hornero-*IEEE Senior Member*

***Abstract*— This study was aimed at exploring phase-amplitude coupling (PAC) patterns of neural activity in dementia due to Alzheimer's disease (AD). For this task, five minutes of spontaneous electroencephalographic (EEG) activity from 22 patients with mild AD and 16 cognitively healthy controls were studied. To assess PAC patterns, phase-locking value was computed between the phase of low frequencies and the power of high frequencies within each sensor. Our results showed that high-frequency gamma power is phase-locked to the alpha peak in EEG signals. Furthermore, statistically significant differences (p<0.05, permutation test) between patients with mild AD and elderly controls were observed at the lower left temporo-parietal area, suggesting that early stages of AD elicit a region-specific decrease of PAC in the neural activity.**

I. Introduction

Several studies have shown that dementia caused by Alzheimer's disease (AD) elicits a number of changes in the resting-state electroencephalographic (EEG) activity [1,2]. In comparison with normal elderly subjects, AD patients exhibited an increase of delta and theta brain oscillation, as well as a decrease of alpha and/or beta rhythms [1]. Using different linear and nonlinear measures, connectivity studies also showed that a disrupted functional brain network can be associated with AD [2]. To date, most of the studies focused on analyzing single-frequency coupling patterns, without exploring cross-frequency interactions. Nevertheless, recent investigations emphasized the functional role of cross-frequency coupling (CFC) in the coordination of neural activity across different spatio-temporal scales [3,4]. Specifically, phase-amplitude coupling (PAC) is aimed at quantifying the dependence between the phase of low frequency oscillations and the amplitude of high frequency rhythms [3,5]. In comparison with other types of CFC, PAC has been linked to plausible physiological mechanisms. Hence, the low frequency phase has been usually associated with local neuronal excitability, whereas the increase of high frequency amplitude is thought to reflect either a global increment in population synaptic activity or selective activation of a cortical subnetwork [3].

Accumulating evidence points out that PAC may play an important role in cognition and neural information processing (e.g. learning and memory) [6]. Nevertheless, only a few recent event-related potential (ERP) and magnetoencephalography (MEG) studies have explored CFC patterns in AD. Their results suggest that CFC can be a helpful tool to characterize pathologic neural dynamics in AD [7-9]. More research is needed to further understand neural coupling patterns in dementia. Therefore, the present research is aimed at exploring PAC patterns of resting-state EEG activity in AD. Specifically, we wanted to examine whether AD affects to the interaction between the phase of the dominant alpha oscillations (7.5-13 Hz) during rest and the amplitude of the gamma band (30-70 Hz).

II. Materials and Methods

A. Subjects and EEG Recordings

The study population was formed by cognitively healthy elderly subjects and patients with dementia due to AD. Socio-demographic and clinical data are indicated in Table I. Patients with probable AD dementia were diagnosed according to the clinical criteria of the NIA-AA (National Institute on Aging and Alzheimer's Association) [10]. Only patients with Mini-Mental State Examination (MMSE) score ranged between 20 and 26 points were included in the study (i.e. mild AD patients). The Bayer Activities of Daily Living Scale (Bayer-ADL) was used to assess functional disability. Cognitive reserve was measured by means of the Spanish version of the Cognitive Reserve Index questionnaire (CRIq) [11], whereas the Memory Alteration Test (M@T) was used to evaluate verbal episodic and semantic memory. Elderly controls were recruited among cognitively healthy subjects with no history of cognitive impairment, neurological illness or psychiatric disorder.

Nonsignificant differences were found in age (U=119.000, p=0.092, Mann-Whitney U-test), gender (χ^2=0.585, p=0.444, Chi-squared test) and education level (χ^2=2.439, p=0.295, Chi-squared test) between controls and mild AD patients. Patients were not taking any medication that could affect EEG signals at the time of the study.

This research was partially supported by: the 'Ministerio de Economía y Competitividad (MINECO)' and FEDER under project TEC2014-53196-R; and the 'Consejería de Educación de la Junta de Castilla y León' under project VA037U16. P. Núñez is in receipt of a 'Promoción de empleo joven e implantación de la Garantía Juvenile n I+D+i' grant from MINECO and the University of Valladolid. J. Gómez-Pilar is in receipt of a PIF-UVA grant from the University of Valladolid.

J. Poza, C. Gómez, M. García, P. Núñez, J. Gomez-Pilar and R. Hornero are with the Biomedical Engineering Group (GIB), Signal Theory and Communications Department, University of Valladolid, Paseo de Belén 15, 47011-Valladolid, Spain (phone: +34 983423000, ext. 5569; fax: +34 983423667; e-mail: jesus.poza@tel.uva.es).

A. Bachiller is with the Research Centre for Biomedical Engineering (CREB), Polytechnic University of Catalonia, Barcelona, Spain (e-mail: alejandro.bachiller@upc.edu).

M. A. Tola-Arribas is with the Department of Neurology, Río Hortega University Hospital, Valladolid, Spain (e-mail: mtola.nrl@gmail.com).

M. Cano is with the Department of Clinical Neurophysiology, Río Hortega University Hospital, Valladolid, Spain (e-mail: mcanopo@saludcastillayleon.com).

TABLE I. SOCIO-DEMOGRAPHIC AND CLINICAL DATA OF THE TWO POPULATIONS ENROLLED IN THE STUDY

Data[a]	Group	
	Controls	*Mild AD patients*
N	16	22
Age (years)	77.2 ± 4.1	79.8 ± 5.9
Gender (male:female)	6:10	11:11
Education level (A:B:C) [b]	1:6:9	5:9:8
MMSE[c]	28.5 ± 1.4	22.6 ± 1.8
Bayer-ADL[d]	1.4 ± 0.9	5.7 ± 1.6
CRIq[e]	10.0 ± 4.8	8.8 ± 5.5
M@T[f]	44.4 ± 4.1	21.8 ± 4.5
IAF (Hz) [g]	9.7 ± 0.6	8.8 ± 1.0

a. Values are given as: mean ± standard deviation
b. A: less than primary education; B: primary education; C: secondary education or above
c. MMSE: Mini-Mental State Examination (range: [0 30])
d. Bayer-ADL: Bayer Activities Daily Living (range: [0 10])
e. CRIq: Cognitive Reserve Index questionnaire (range: [0 25])
f. M@T: Memory Alteration Test (range: [0 50])
g. IAF: Individual Alpha Frequency

Participants and patients' caregivers were informed on the aims and experimental protocol of the research. All of them gave their informed consent to participate in the study. The Ethics Committee of the University Hospital Río Hortega (UHRH, Valladolid, Spain) endorsed the study protocol, which was designed in accordance with the ethical considerations of the World Medical Association (Declaration of Helsinki).

B. EEG Recordings

EEG signals were acquired using a 19-channel EEG system (XLTEK®, Natus Medical), located at the Department of Clinical Neurophysiology of the UHRH. Specifically, electrodes were placed on the scalp according to the International 10-20 System. The following standard electrode sites were used: F_{p1}, F_{p2}, F_z, F_3, F_4, F_7, F_8, C_z, C_3, C_4, T_3, T_4, T_5, T_6, P_z, P_3, P_4, O_1 and O_2. The sampling frequency was 200 Hz. During EEG acquisition, subjects were instructed to stay relaxed, awake, and keep their eyes closed. EEG recordings were continuously monitored to avoid drowsiness.

According to the aforementioned protocol, 5 minutes of spontaneous EEG activity were recorded for every subject. For each EEG recording, the following artifact rejection procedure was applied: (i) application of a notch filter to remove 50 Hz noise and a band-pass filter between 2 and 90 Hz; (ii) segmentation of EEG recordings into 5-s length trials; and (iii) visual selection of artifact-free EEG trials of 5-s length. In order to avoid the influence of the number of trials on the results, the first 18 artifact-free EEG trials of 5-s length were selected for every subject for further analysis. This amount of data is similar to that used in previous CFC studies [5,8], which lets us perform a reliable CFC analysis.

C. Cross-Frequency Coupling

For each artifact-free EEG trial, a specific CFC filtering was carried out to analyze PAC patterns between the low and high frequencies. EEG trials were band-pass filtered using a zero phase-lag finite impulse response (FIR) filter between ±2.5 Hz of the dominant alpha peak. The alpha peak was computed as the individual alpha frequency (IAF) in each subject (see Table I) [12]. Gamma oscillations were extracted by applying a zero phase-lag FIR filter from 30 to 70 Hz.

Diverse methods can be found in the literature to study PAC [16]. Among them, the phase-locking value (PLV) has been highlighted as one of the most robust and sensitive methods for exploring CFC interactions [13]. Hence, PAC patterns were investigated by computing the phase-locking value (PLV) between the low frequency signal and the power at gamma band for each EEG sensor [14]. For this task, the instantaneous phase of the low frequency filtered signal, (i.e. $\phi_{\alpha-\text{peak}}[k,j]$) and the amplitude of the gamma band filtered signal (i.e. $A_\gamma[k,j]$) were extracted by means of the analytic signals for each trial *j*, which were calculated using the Hilbert transform. Next, a second filtering was applied to compute the low frequency component of the high frequency amplitude envelope $A_\gamma[k,j]$, from which the phase was calculated using again the Hilbert transform (i.e. $\phi_{A_\gamma}[k,j]$). Finally, PAC for each trial was computed as

$$PAC_{\alpha-\text{peak}\rightarrow\gamma}[j]=\left|\frac{1}{K}\sum_{k=1}^{K}\exp\left\{i\cdot\left(\phi_{\alpha-\text{peak}}[k,j]-\phi_{A_\gamma}[k,j]\right)\right\}\right| \quad (1)$$

where *K* represents the number of time points in each trial.

E. Statistical Analysis

In a first step, we assessed whether statistically significant PAC values were obtained for each subject. For this task, surrogate data were generated by randomly shifting the phases of trials [15]. Repeating this procedure 1000 times, we obtained a distribution of PAC values. The proportion of PAC values obtained from the randomization procedure above the PAC value to be tested was used to compute the *p*-value and the corrected PAC values.

In a second step, we conducted a population-based statistical analysis. In this regard, between-group sensor-level statistics over corrected PAC values were assessed using a multiple comparison nonparametric permutation test (1000 permutations) [16].

Signal processing and statistical analyses were performed using the software packages Matlab (version 8.4, Mathworks, Natick, MA) and SPSS Statistics (version 20, IBM Corp, Armonk, NY).

III. RESULTS

A. Power Analyses

It is noteworthy that a clear peak on low frequency power is required in order to obtain a reliable CFC [4]. The grand-averaged power spectral density for controls and patients with mild AD is shown in Fig. 1. A clear peak in the alpha band can be appreciated for both groups, whereas no dominant frequency component was observed in the gamma band.

Sensor-level power analyses in Fig. 2 confirmed the previous results. Power around the alpha peak was mainly distributed on posterior brain regions for both groups (Fig.

2.a). Power in gamma band showed a different topography (Fig. 2.b), with maximum values in the occipital and temporal brain regions.

B. *Phase-Amplitude Coupling Analyses*

The sensor-level PAC patterns for both groups are summarized in Fig. 3. Interestingly, corrected PAC values were higher in the posterior brain areas both for controls and patients with mild AD, when compared to other brain regions. The statistical analyses revealed that patients with mild AD displayed a statistically significant decrease (p<0.05) of corrected PAC values at T5, when compared to controls.

The strong coupling found for controls in the posterior brain regions of both groups can be also appreciated in the histogram of Fig. 4. Thus, the highest percentage of subjects with statistically significant PAC values (p<0.05) was obtained for the sensors: O1, O2, P4, T4, and T5.

IV. Discussion

In line with previous EEG and MEG studies [1,12], we observed the slowing of the power spectrum commonly observed in AD when compared to normal aging (see Fig. 1). Likewise, our results showed that gamma power is phase-locked to oscillations around the alpha band peak. These results are in agreement with previous MEG studies that also observed a posterior PAC pattern in healthy human subjects at rest, mainly in the left hemisphere of the brain [5].

More interestingly, our findings suggested that early AD could be associated with a region-specific decrease of phase-amplitude coupling. In line with our research, a previous MEG study found a decrease of amplitude-based CFC in AD patients in comparison with controls between beta band and all other bands in several brain regions, which included the hippocampus and different brain areas of the default mode network [9]. In a resting-state EEG study, amplitude-amplitude coupling patterns in AD were assessed [7]. They found that AD was accompanied by a progressive reduction of delta modulation of the beta band [7]. Abnormalities in the PAC patterns of patients with mild AD might be related with an early disrupted mechanism of cognitive systems. In a recent ERP study, subjects with amnestic mild cognitive impairment (MCI) exhibited a hyper cross-synchronization in several frequency pairs compared to normal controls [8], which was related to the higher cognitive effort required for MCI patients to accurately perform the auditory oddball task. It was hypothesized that this increase of PAC values in MCI patients could reflect the cognitive overload of attention and working memory systems [8].

Several technical and clinical considerations of the current study merit further comment. Firstly, it would be interesting both to increase the sample size and to extend our analyses to prodromal dementia stages, such as MCI or preclinical AD. Secondly, future studies should explore whether the observed PAC patterns at the sensor-level are also found at the source-level. Thirdly, our study was focused on analyzing PAC between alpha phase and gamma power using PLV. Further research should be devoted to studying other forms of CFC across frequencies in AD, such as amplitude-amplitude, phase-phase or phase-frequency CFC.

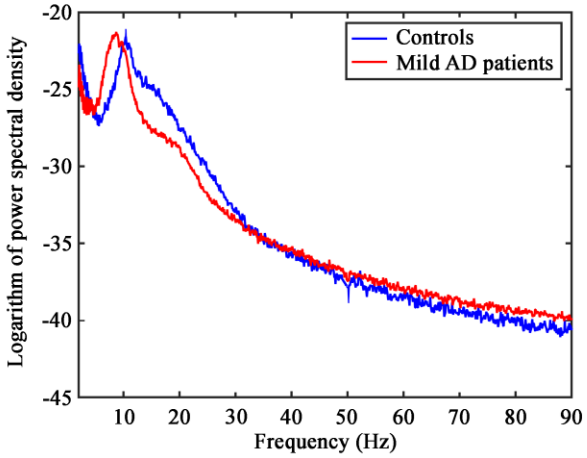

Figure 1. Grand-average of log-transformed power spectra for each group (C: controls; mild-AD: patients with mild AD).

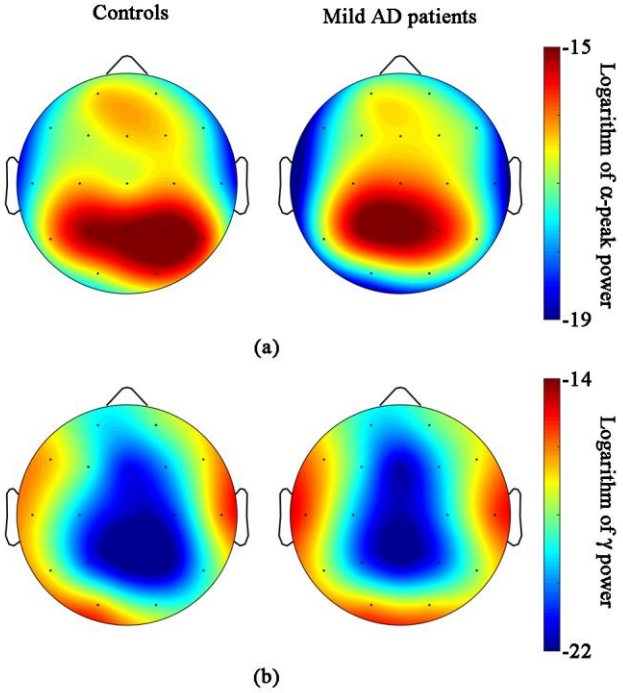

Figure 2. Sensor-level topography of the log-transformed power for the low- and high-frequency bands for each group (controls and patients with mild AD). (a) Log-trasformed power for the frequency band center on the alpha peak (IAF±2.5 Hz). (b) Log-transformed power for the gamma band (30-70 Hz).

Likewise, future studies should be carried out to analyze other PAC measures, such as the mean vector length or the Kullback-Leibler distance [13], and to explore PAC patterns between other low- (i.e. delta and theta) and high-frequency bands (i.e. beta and gamma). Finally, the debate on the directionality of CFC has been brought into focus by recent studies [17,18]. It has been usually considered that a unidirectional interaction between alpha phase and gamma power should exist, but recent findings suggest rather that alpha-gamma interaction would be governed by a causal relationship [17,18]. Consequently, future studies should

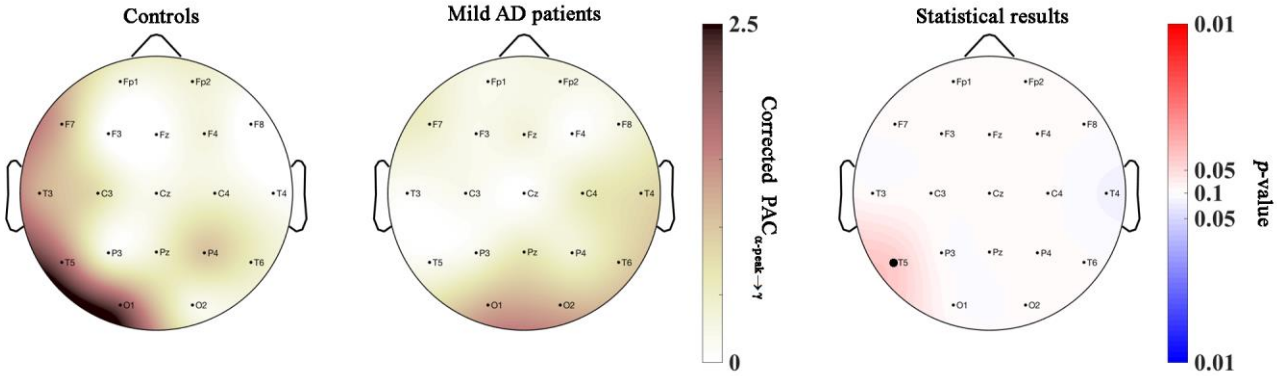

Figure 3. Sensor level topography of corrected PAC values averaged over sensors for each group (controls, left column, and patients with mild AD, central column) and statistical results of between-group comparisons (right column). Hot (cold) colors in right column represent a higher (smaller) coupling in controls than in mild AD patients. Dots (•) indicate sensors showing statistically significant differences (p<0.05, permutation test).

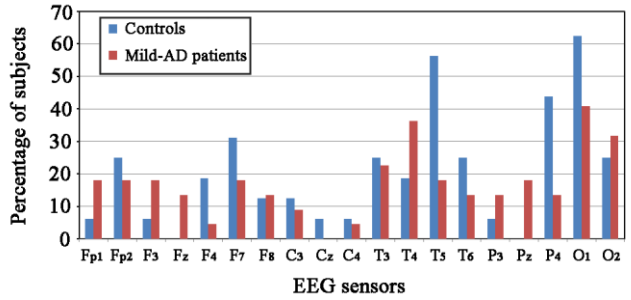

Figure 4. Histogram (percentage) of controls and patients with mild AD showing a statistically significant phase-amplitude coupling (p<0.05, surrogate data test) for each EEG sensor.

assess the role of the feedback mechanism in which gamma drives the alpha entrainment on the characterization of AD neural dynamics.

V. Conclusion

Our findings support the results of previous MEG studies that observed a significant CFC interaction between gamma power and alpha phase in posterior brain regions. Furthermore, they suggest that early AD is accompanied by an abnormal phase-to-amplitude coupling between the alpha-peak and the gamma band. Future studies will be carried out to analyze the AD-related abnormalities in other forms of CFC and to elucidate the role of causal CFC interactions in dementia.

Acknowledgment

This research would have not been possible without the help and cooperation of the patients from UHRH and their caregivers, as well as the healthy volunteers.

References

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

[2] C. Babiloni, R. Lizio, N. Marzano, P. Capotosto, A. Soricelli, A. I. Triggiani, *et al.*, "Brain neural synchronization and functional coupling in Alzheimer's disease as revealed by resting state EEG rythms," *Int. J. Psychophysiol.*, vol. 103, pp. 88–102, 2016.

[3] R. T. Canolty and R. T. Knight, "The functional role of cross-frequency coupling," *Trends Cogn. Sci.*, vol. 14, pp. 506–515, 2010.

[4] J. Aru, J. Aru, V. Priesemann, M. Wibral, L. Lana, G. Pipa, W. Singer, and R. Vicente, "Untangling cross-frequency coupling in neuroscience," *Curr. Opin. Neurobiol.*, vol. 31, pp. 51–61, 2015.

[5] D. Osipova, D. Hermes, and O. Jensen, "Gamma power is phase-locked to posterior alpha activity," *PLoS One*, vol. 3, p. e3990, 2008.

[6] J. E. Lisman and O. Jensen, "The theta-gamma neural code," *Neuron*, vol. 77, pp. 2001–1016, 2103.

[7] F. J. Fraga, T. H. Falk, P. A. M. Kanda, and R. Anghinah, "Characterizing Alzheimer's disease severity via resting-state awake EEG amplitude modulation analysis," *PLoS One*, vol. 8, p. e72240, 2013.

[8] S. I. Dimitriadis, N. A. Laskaris, M. P. Bitzidou, I. Tarnanas, and M. N. Tsolaki, "A novel biomarker of amnestic MCI based on dynamic cross-frequency coupling patterns during cognitive brain responses," *Front. Neurosci.*, vol. 9, p. 350, 2015.

[9] M. A. A. Engels, M Yu, H Arjan, P. Scheltens, W. M. van der Flier, E. C. W. van Straaten, and C. J. Stam, "MEG cross-frequency analysis in patients with Alzheimer's disease," *Alzheimers Dement.*, vol. 12 (Suppl.), pp. P1087–P1088, 2016.

[10] G. M. McKhann, D. S. Knopman, H. Chertkow, B. T. Hyman, C. R. Jr. Jack, C. H. Kawas, *et al.*, "The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimers Dement*, vol. 7, pp. 263–269, 2011.

[11] L. Rami, C. Valls-Pedret, D. Bartrés-Faz, C. Caprile, C. Solé-Padullés, M. Castellvi, J. Olives, B. Bosch, and J. L. Molinuevo, "Cognitive reserve questionnaire. Scores obtained in a healthy elderly population and in one with Alzheimer's disease," *Rev. Neurol.*, vol. 52, pp. 195–201, 2011 (in Spanish).

[12] J. Poza, R. Hornero, D. Abásolo, A. Fernández, and M. García, "Extraction of spectral based features from MEG background oscillations in Alzheimer's disease," *Med. Eng. Phys.*, vol. 29, pp. 1073–1083, 2007.

[13] A. B. Tort, R. Komorowski, H. Eichenbaum, and N. Kopell, "Measuring phase-amplitude coupling between neuronal oscillations of different frequencies," *Neuroimage*, vol. 140, pp. 76–82, 2015.

[14] W. D. Penny, E. Duzel, K. J. Miller, and J. G. Ojemann, "Testing for nested oscillation," *J. Neurosci. Methods*, vol. 174, pp. 50–61, 2008.

[15] V. Jirsa and V. Müller, "Cross-frequency coupling in real and virtual brain networks," *Front. Comput. Neurosci.*, vol. 7, p. 78, 2013.

[16] T. E. Nichols and A. P. Holmes, "Nonparametric permutation tests for functional neuroimaging: a primer with examples," *Hum. Brain Mapp.*, vol. 15, pp. 1–25, 2001.

[17] R. F. Helfrich, C. S. Herrmann, A. K. Engel, and T. R. Schneider, "Different coupling modes mediate cortical cross-frequency interactions," *Neuroimage*, vol. 140, pp. 76–82, 2015.

[18] H. Jiang, A. Bahramisharif, M. A. van Gerven, and O. Jensen, "Measuring directionality between neuronal oscillations of different frequencies," *Neuroimage*, vol. 118, pp. 359–367, 2015.