Alterations of Effective Connectivity Patterns in Mild Cognitive Impairment: An MEG Study

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Abstract– Neuroimaging techniques have demonstrated over the years their ability to characterize the brain abnormalities associated with different neurodegenerative diseases. Among all these techniques, magnetoencephalography (MEG) stands out by its high temporal resolution and noninvasiveness. The aim of the present study is to explore the coupling patterns of resting-state MEG activity in subjects with mild cognitive impairment (MCI). To achieve this goal, five minutes of spontaneous MEG activity were acquired with a 148-channel whole-head magnetometer from 18 MCI patients and 26 healthy controls. Inter-channel relationships were investigated by means of two complementary coupling measures: coherence and Granger causality. Coherence is a classical method of functional connectivity, while Granger causality quantifies effective (or causal) connectivity. Both measures were calculated in the five conventional frequency bands: delta (δ, 1-4 Hz), theta (θ, 4-8 Hz), alpha (α, 8-13 Hz), beta (β, 13-30 Hz), and gamma (γ, 30-45Hz). Our results showed that connectivity values were lower for MCI patients than for controls in all frequency bands. However, only Granger causality revealed statistically significant differences between groups (p-values < 0.05, FDR corrected Mann-Whitney U-test), mainly in the beta band. Our results support the role of MCI as a disconnection syndrome, which elicits early alterations in effective connectivity patterns. These findings can be helpful to identify the neural substrates involved in prodromal stages of dementia.

Keywords–Mild Cognitive Impairment, magnetoencephalography (MEG), Granger causality, coherence, connectivity, neuroimaging.

1. INTRODUCTION

The concept of mild cognitive impairment (MCI) was first mentioned in the literature in the late 80s, as the result of a growing concern in portraying the early stages of dementia [1]. However, it was not until 1995 that Petersen defined it as an independent clinical condition [2, 3]. MCI is described as a disorder characterized by a cognitive decline higher than expected by age and education, but insufficient to meet the criteria for the diagnosis of dementia [4]. Even if cognitive activity is impaired, these patients maintain their independence in their functional and social skills. Worldwide studies recently estimated the overall prevalence of MCI within a range from 12% to 18% for elderly people over 60 years [5]. Some of them remain stable or return to normal over time, but more than 50% progress to dementia [6]. The conversion rate to dementia due to Alzheimer's disease (henceforth AD) is approximately 15% per year [7], although MCI can be also a prodromal stage of other dementia subtypes, such as vascular dementia [8], dementia with Lewy body [9] or Parkinson's disease [10]. For this reason, current perspectives on MCI interpret this condition as a risk state and/or prodromal stage for various types of dementia, and not as an independent clinical condition [11, 12]. Pharmacological intervention is currently unsuccessful in the treatment of MCI or dementia. However, an early and conclusive diagnosis is necessary, since the medication used to delay the symptoms and optimize the overall clinical and functional condition of the patient is more effective in the first stages of dementia [13, 14].

During the last decades, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have been used to investigate cerebral changes in AD and MCI. Previous fMRI studies reported impairments in brain functional activity in the default mode network of MCI subjects [15, 16]. During associative encoding of picture-word pairs, MCI subjects exhibited increased fMRI responses in the posterior hippocampal, parahippocampal and fusiform regions [17]. On the other hand, PET studies suggested that changes in glucose

metabolism might be useful to predict the conversion from MCI subjects to AD [18]. Other authors demonstrated that the retention of an amyloid-imaging PET tracer in MCI subjects is at an intermediate level between healthy controls and AD patients [19]. PET and fMRI exhibit a good spatial accuracy, but both offer a poor temporal resolution to study brain dynamics. On the other hand, electroencephalography (EEG) and magnetoencephalography (MEG) have much higher temporal resolution than fMRI and PET, allowing the real-time recording of neural activity. EEG and MEG have also proved their usefulness to characterize the brain abnormalities associated with MCI and AD [20–37]. Compared to EEG, MEG offers reference-free recordings. Additionally, the effect of the heterogeneous conductivity of the skull and scalp is significantly lower for magnetic fields. Finally, MEG provides better spatial resolution than conventional EEG. Due to the aforementioned advantages of MEG over other neuroimaging modalities, neural dynamics in MCI were evaluated in the current study using this non-invasive technique.

The characterization of AD and MCI using MEG has been addressed in the last decades applying different signal processing techniques. Until the introduction of methods derived from nonlinear dynamics, MEG signals were explored with linear techniques based on spectral analyses [26, 32]. The most common marker in AD and MCI patients is a slowing of MEG activity during resting-state. In particular, MCI subjects showed intermediate median frequency values between AD patients and controls [26]. Several non-linear analysis methods suggested that AD and MCI elicit a complexity decrease in spontaneous brain activity as well as an increase of regularity [27, 28]. Using Lempel-Ziv complexity, Fernández *et al.* [27] showed that AD patients and controls exhibit a parallel tendency to diminished complexity values as a function of age, but MCI patients did not show such normal tendency. All these methods (both the spectral and the non-linear ones) measure local activation patterns in individual sensors. However, it has become clear that simple activation studies are no longer

sufficient for a full characterization of brain dynamics [36]. For this reason, attention has shifted to coupling analyses during the last years. For instance, Escudero *et al.* [25] found that AD and MCI cause slight alterations in the MEG connectivity. Another study [29] revealed significant differences between MCI subjects and controls in the beta frequency band for both coherence (*COH*) and synchronization likelihood (*SL*). A more recent measure, called phase lag index (*PLI*), revealed that AD is associated with a synchronization decrease in the lower alpha and beta bands [34]. Bajo *et al.* [22] analyzed the MEG activity obtained during a memory task in 22 MCI subjects and 19 controls by means of *SL*. Their results revealed an increase in long distance inter-hemispheric connections in MCI, but a decrease in anteroposterior functional connectivity [22]. All these coupling methods (*COH*, *SL*, *PLI*, etc.) measure functional connectivity (i.e. dependencies between remote neurophysiological events) [37]. However, although awareness of the existence of a connection is important, mapping the directional relationships is essential to fully characterize information flow dynamics in MCI. For this reason, measures of effective or causal connectivity (i.e. the influence that one neural system exerts over another) are needed to overcome the limitations of the aforementioned analyses [37].

The aim of this study is to analyze MEG connectivity patterns in MCI by means of *COH*, a classical measure of functional connectivity, but also using Granger causality (*GC*), a measure of effective connectivity. To our knowledge, this is the first study that uses an effective connectivity measure to characterize the MEG brain dynamics in MCI. We want to address the following research questions: (i) Can these measures (*COH* and *GC*) be useful to identify MCI as a disconnection syndrome?; (ii) Can *GC* provide further insights about the abnormal connectivity patterns in MCI to those obtained using *COH*?; (iii) Which measure provides a better discrimination between controls and MCI subjects?

2. MATERIALS AND METHODS

2.1. Subjects

In this study, MEG signals were recorded from 44 subjects: 18 patients diagnosed with MCI and 26 controls without past or present neurological disorders. Clinical diagnosis was determined through psychiatric and neurological examinations at San Carlos University Hospital (Madrid, Spain). MCI patients were diagnosed according to the National Institute on Aging-Alzheimer Association (NIA-AA) criteria [11]. Based on their cognitive profile, all of them were classified as amnestic MCI patients. Besides meeting the core clinical criteria for MCI, patients also exhibited significant hippocampal atrophy according to the evaluation of an experienced neuroradiologist, who was blinded to the clinical outcome. Consequently, patients were categorized as "MCI due to AD intermediate likelihood" [11].

For each subject, cognitive grade was assessed by means of the Mini Mental State Examination (MMSE) test [38], while functional status was evaluated with the Global Deterioration Scale/Functional Assessment Staging (GDS/FAST) system [39]. The main clinical and socio-demographic data are summarized in Table 1. There were not statistically significant differences between both populations in terms of age ($p > 0.05$, Mann-Whitney *U*-test) and gender ($p > 0.05$, Chi-square test).

The local Ethics Committee of San Carlos University Hospital approved this investigation. Controls and patients' caregivers signed the informed consent for the participation in this study, which was conducted in accordance with the Declaration of Helsinki guidelines.

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2.2. MEG acquisition and pre-processing

Continuous resting-state MEG activity was acquired by qualified technicians using a 148-channel whole head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) placed in a magnetically shielded room at the MEG Centre Dr. Pérez-Modrego (Madrid, Spain). The participants laid awake in a stretcher with closed eyes. For each subject, five minutes of MEG data were acquired at a sampling frequency of 678.17 Hz. A process of down-sampling by a factor of four was accomplished to reduce the data length, with a subsequent sampling rate of 169.55 Hz.

For each MEG recording, the following pre-processing procedure was applied: (i) application of independent component analysis (ICA) to minimize the presence of artifacts; (ii) data filtering with a 1-65 Hz band-pass filter and a 50 Hz notch filter; (iii) visual inspection to select artifact-free epochs of 5 s (848 samples); and (iv) normalization of the artifact-free epochs to have zero-mean and standard deviation of 1. Signal pre-processing was conducted using Matlab (version 8.4, Mathworks, Natick, MA).

2.3. Connectivity measures

The study of neural interactions seeks to understand how different regions of brain communicate with each other. In this research, we focused on two complementary points of view, which have been developed to analyze neural connections: *COH* and *GC*. Both measures were computed for the five conventional frequency bands: delta (δ, 1-4 Hz), theta (θ, 4-8 Hz), alpha (α, 8-13 Hz), beta (β, 13-30 Hz), and gamma (γ, 30-45 Hz). The result of computing each measure for all pair-wise combinations of channels was an $M \times M$ matrix (M = 148), where each entry M_{jk} contains the *COH* or *GC* value between the channels j and k. The matrix was symmetric for *COH*, whereas it was asymmetric for *GC*, as it is an effective connectivity measure. Afterwards, connectivity results were grouped into eight brain areas (see Figure 1), and intrahemispheric (i.e. between two different areas within one hemisphere)

and interhemispheric (i.e. between homologue regions of two hemispheres) connectivity patterns were calculated. The connectivity value between two regions was estimated averaging values for pairs of sensors, where each sensor was in a different brain region.

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2.3.1. Coherence (COH)

COH is a well-known method to assess brain connectivity. It measures the existing linear pair-wise correlations between two time series in a specific frequency band. This method has been widely used to study the coupling patterns in AD and MCI [23, 29, 31]. However, *COH* is not able to provide information about the direction in which the neurophysiological connections are addressed.

Let $x_j(t)$ and $x_k(t)$ the time series from two MEG channels j and k. Their complex Fourier transforms can be expressed as:

$$X_j(f) = a_j \exp(i\varphi_j), \tag{1}$$

$$X_k(f) = a_k \exp(i\varphi_k), \tag{2}$$

where a_j and a_k are the amplitudes, while φ_j and φ_k are the phases of the time series at a given frequency f. The power auto spectral density function $S_{jj}(f)$ of channel j (analogous expression for channel k) and the cross-spectral density function $S_{jk}(f)$ for channels j and k are defined as [40]:

$$S_{jj}(f) = \left\langle X_j(f) X_j^*(f) \right\rangle, \tag{3}$$

$$S_{jk}(f) = \left\langle X_j(f) X_k^*(f) \right\rangle, \tag{4}$$

where * designates the complex conjugate and $\langle \cdot \rangle$ the inner product.

COH between channels j and k is defined as the absolute value of the normalized cross-spectrum [29, 40]:

$$COH_{jk}(f) = \left| \frac{S_{jk}(f)}{\sqrt{S_{jj}(f) S_{kk}(f)}} \right|^2 = \left| \frac{\langle a_j a_k \exp(i\Delta\varphi) \rangle}{\sqrt{\langle a_j^2 \rangle \langle a_k^2 \rangle}} \right|^2, \quad (5)$$

where $\Delta\varphi$ is the instantaneous phase difference between the time series $x_j(t)$ and $x_k(t)$. *COH* values range from 0 to 1, indicating the degree of connectivity between the aforementioned two signals. In our study, the *COH* algorithm was applied to each pairwise combination of MEG channels.

2.3.2. Granger Causality (GC)

Effective (or causal) connectivity measures emerge as key tools to deal with the evaluation of the directionality in which a neurological event is exerted [37]. One of the most popular measures of causal connectivity is the *GC*, which has been applied in a wide range of areas, such as economy [41] or meteorology [42]. The idea of causality was proposed by Wiener in 1956 [43]: one signal $x_j(t)$ is called causal to other $x_k(t)$ if the prediction of the second one is improved by adding past information of the first one, compared to past information of $x_k(t)$ only. Subsequently, Granger reformulated this statement in terms of autoregressive models [44]. Let $x_j(t)$ and $x_k(t)$ denote the time series from two MEG channels j and k. The bivariate autoregressive models for $x_j(t)$ and $x_k(t)$ could be written as [45]:

$$x_j(t) = \sum_{u=1}^{p} A_{11}(u) x_j(t-u) + \sum_{u=1}^{p} A_{12}(u) x_k(t-u) + \gamma_j(t), \quad (6)$$

$$x_k(t) = \sum_{u=1}^{p} A_{21}(u) x_j(t-u) + \sum_{u=1}^{p} A_{22}(u) x_k(t-u) + \gamma_k(t), \quad (7)$$

where $\gamma_j(t)$ and $\gamma_k(t)$ are the prediction errors at each time instant and $A(u)$ are model parameters. If the variance of $\gamma_j(t)$, denoted by Γ_j, is reduced by the inclusion of the x_k terms in the first equation, then it is possible to say that x_k causes x_j.

As neurophysiological time series contain relevant information in the frequency domain, causal interactions are usually represented with a spectral approach. Geweke [46]

reconstructed the time-domain Wiener-Granger Causality into its spectral configuration. This current study relies on this spectral representation for the analysis of MEG causality. To examine the causal relations in the spectral domain, the Fourier transforms of the bivariate autoregressive models of equations (6) and (7) can be represented as follows [45]:

$$\begin{pmatrix} A_{11}(f) & A_{12}(f) \\ A_{21}(f) & A_{22}(f) \end{pmatrix} \begin{pmatrix} X_1(f) \\ X_2(f) \end{pmatrix} = \begin{pmatrix} E_1(f) \\ E_2(f) \end{pmatrix}, \tag{8}$$

where the elements of $\boldsymbol{A}(f)$ matrix are:

$$A_{lm}(f) = \delta_{lm} - \sum_{n=1}^{p} A_{lm}(j) \exp(-i2\pi fn), \text{ with } \delta_{lm} = \begin{cases} 1 & \text{if } l = m \\ 0 & \text{if } l \neq m \end{cases} \tag{9}$$

Multiplying both sides of the equation by the inverse of $\boldsymbol{A}(f)$ matrix, the following expression is obtained:

$$\begin{pmatrix} X_1(f) \\ X_2(f) \end{pmatrix} = \begin{pmatrix} H_{11}(f) & H_{12}(f) \\ H_{21}(f) & H_{22}(f) \end{pmatrix} \begin{pmatrix} E_1(f) \\ E_2(f) \end{pmatrix}, \tag{10}$$

where $\boldsymbol{H}(f)$ is called the spectral transfer matrix.

Finally, *GC* from signal $x_j(t)$ to $x_k(t)$ is given by [47]:

$$GC_{j \to k}(f) = \ln\left(\frac{S_{kk}(f)}{\overline{H}_{kk}(f) \cdot \Gamma_k \cdot \overline{H}^*_{kk}(f)} \right), \tag{11}$$

where $S_{kk}(f)$ is the autospectrum of $x_k(t)$ and $\overline{H}_{kk}(f) = H_{kk}(f) + \left(\gamma_k \big/ \Gamma_k \right) H_{kj}(f)$.

In pursuance of a best fit of the real system to the autoregressive model, an appropriate model order p should be determined. As the model order represents the total number of past samples considered, a low value provides a sparse representation of the data, while high model values overestimate the system. In this research, an autoregressive model order of p = 28 was selected from the minimum obtained after applying the Akaike and the Bayesian Information Criterion [48].

2.4. Statistical analysis

Firstly, a descriptive analysis was carried out to study the distribution of the connectivity results. Kolmogorov–Smirnov and Shapiro–Wilks tests were used to evaluate the normality of the data, whereas Levene test was employed to assess the homogeneity of variances. As *COH* and *GC* results did not meet the parametric test assumptions, statistical differences between MCI patients and control subjects were evaluated with the Mann-Whitney *U*-test. In order to deal with the multiple comparisons problem, resampling-based false discovery rate (FDR) was applied [49]. Finally, receiver operating characteristic (ROC) curves, with a leave-one-out cross-validation procedure, were used to assess the ability of *COH* and *GC* to discriminate MCI patients from elderly controls. Statistical analyses were performed using Matlab (version 8.4, Mathworks, Natick, MA).

3. RESULTS

Connectivity patterns obtained for each frequency band are presented in Figures 2 (*COH*) and 3 (*GC*). For both figures, the first column shows the results for the healthy group, while the outcomes for MCI group are presented in the second column. Finally, between-groups statistical results are illustrated in the third column. Note that only statistically significant differences (FDR-corrected Mann-Whitney *U*-test) between MCI and control groups are displayed using a color-code: red color tones indicate significant connectivity increases in MCI patients in comparison with controls, whereas blue color tones denote significant decreases.

Our *COH* results showed that MEG activity in MCI patients is characterized by an overall connectivity decrease in all frequency bands. Statistically significant differences between groups were found before the FDR correction for the following interactions: between left-frontal and right-frontal (θ band), between right-lateral and right-posterior (θ band), between

left-lateral and left-posterior (α and β bands), and finally between left-central and left-posterior at (β band). However, no connections remain statistically significant after FDR correction, as Figure 2 shows. *GC* results supported the connectivity loss previously found using *COH* measure. With this effective connectivity measure, statistically significant differences were obtained in all frequency bands, with the exception of δ band (see Figure 3). Particularly, almost all interhemispheric and intrahemispheric connections remain significant after FDR correction in β band.

DISPLAY FIGURES 2 AND 3 AROUND HERE

ROC curves with a leave-one-out cross-validation procedure were used to assess the ability of each intrahemispheric and interhemispheric connectivity value to classify MCI patients and control subjects. The highest accuracy for *COH* results was achieved in γ band for the interhemispheric connection between central areas: 77.27% (sensitivity = 44.44%; specificity 100%; area under the ROC curve = 0.72). With *GC*, the highest accuracy values (accuracy = 79.54%; sensitivity = 77.78%; specificity 80.77%; area under the ROC curve = 0.83) were reached for two different connections in β band: from left-posterior to right-posterior and from left-anterior to left-central.

4. DISCUSSION AND CONCLUSIONS

The goal of this study was to evaluate the presence of disconnection patterns in the prodromal stage of dementia. For that purpose, a measure of functional connectivity (*COH*) and one of effective connectivity (*GC*) were applied to spontaneous MEG recordings from 18 MCI patients and 26 control subjects.

4.1. MCI as a disconnection syndrome

The first research question pointed out in the introduction posed the issue whether *COH*

and *GC* can be useful to identify MCI as a disconnection syndrome. Our *COH* results revealed that MCI group is characterized by a global decrease of functional connectivity in all frequency bands. However, no significant differences were found between MCI and control groups. Evidence for a functional connectivity loss in AD comes from several previous studies. For instance, Besthorn *et al.* [23] found a *COH* decrease in AD. This effect was most pronounced in frontal and central EEG channels in θ, α and β frequency bands [23]. An EEG study revealed diminished *SL* values for AD patients in all frequency bands, in comparison with subjects with subjective memory complaints [33]. However, *SL* significantly decreased only in the 14–18 and 18–22 Hz bands [33]. Other functional metrics, such as *PLI* [34, 50] and global field synchrony (*GFS*) [30] confirmed the disconnection syndrome in AD. Although the study of neural coupling patterns in MCI is less common, some previous studies also suggested that this disorder is also associated with disrupted brain networks. Koenig *et al.* [30] showed that MCI is associated with decreased *GFS* values in α, β and γ frequency bands. A global connectivity decrease in β band was also reported using *SL* [29]. The same measure revealed significant differences between MCI subjects and elderly controls in δ and α at frontoparietal electrode pairs [20]. Other study showed decreased levels of local and large-scale connectivity in δ and θ during eyes-closed condition [35]. These studies agree with our results and support the notion that the functional disconnection between brain regions is a characteristic feature of MCI [35].

Besides that, our *GC* results also suggest that the brain dysfunction of MCI patients is associated with reduced values of effective or causal connectivity. To date, there are only a few MCI studies that analyzed the causal interactions between different brain regions. Dauwels *et al.* [24] applied different connectivity measures based on *GC*, observing a reduction of EEG synchrony in MCI patients with most measures. In a previous fMRI study [51], a loss of causal interactions among the resting state networks was reported in MCI

patients compared with normal controls. Babiloni *et al.* [21] highlighted the loss of the parieto-to-frontal coupling, suggesting that the posterior regions operate over the frontal ones in MCI. However, this disrupted coupling is also a significant feature in AD and in dementia with Lewy bodies [52, 53].

In sum, our research and all these previous studies support the hypothesis that AD, and also MCI, can be identified as disconnection syndromes [54]. This decrease in functional and effective connectivity is typically identified with neuronal loss and neocortical disconnection, which gradually increment as dementia progresses [23].

4.2. Abnormal connectivity patterns in MCI

The second research question was aimed at analyzing whether *GC* provides more information than *COH* about the abnormal connectivity patterns in MCI. Our results suggest that *GC* is more adequate than *COH* to characterize the neural coupling patters in MCI. *GC* provides information on the directionality of the connections, but it also showed statistical differences between groups that *COH* could not detect. Particularly, statistically significant differences were found in all frequency bands with the exception of δ band. Interhemispheric *GC* decrements were found between frontal areas (both directions) in θ, α and β, from left central to right central in θ, between posterior brain regions in α and β, and finally between temporal areas (from right to left in θ, and in both directions in α, β and γ). This interhemispheric disconnection syndrome may be associated with the memory and cognitive deficits in AD and MCI [55].

On the other hand, statistically significant differences in intrahemispheric couplings were found mainly between frontal, lateral and posterior areas, but also from these aforementioned areas to central regions, and between posterior and frontal regions. These results agree with previous EEG, MEG and fMRI studies, which showed decreased levels of connectivity between different brain areas [21, 31, 56]. An fMRI study revealed that posterior areas and

medial temporal lobes show remarkable disturbances in neuronal communication in early phases of dementia [56]. These alterations can be due to the deposition of neurofibrillary tangles and to brain atrophy [56]. However, other authors suggested that these changes may also affect other areas [57, 58]. Moretti *et al.* [31] reported a *COH* decrease of intrahemispheric fronto-parietal couplings at both hemispheres. Babiloni *et al.* [21] found that parietal to frontal direction of the information flux within EEG functional coupling was stronger in controls than in MCI subjects, specifically at α and β rhythms. Actually, this disconnection effect was still significant when grey matter volume is included in the analyses as a covariate [59]. This fact may suggest that this connectivity loss contributes to the impairment of episodic memory retrieval in MCI patients [59].

The aforementioned studies support evidences for considering MCI as a disconnection syndrome, although the involved brain areas differ. This disparity on the results could be due to the heterogeneity of MCI, the different neuroimaging techniques used to measure the brain activity, the different connectivity methods applied, or a combination of these factors. Notwithstanding, all these studies seem to link up MCI with a connectivity loss, at least at α and β bands. Our results confirmed these findings. These abnormal connectivity patterns may be due to the brain structural changes suffered by MCI patients: decrease in the size of the hippocampus, high atrophy in the medial temporal lobe, white matter damage in posterior areas, and loss of the global volume of the gray matter [60–63].

4.3. Discrimination of controls and MCI patients

We raised the third research question about which measure (*COH* or *GC*) provides a better discrimination between MCI and control groups. For this purpose, ROC curves were calculated for each connection and frequency band. Our results showed that the highest classification accuracy obtained with *GC* (79.54%) was slightly better than *COH* results (77.27%). The best classification results were obtained in the β band. Previous studies

reported that this frequency range is related with the impairment of cognitive functions, such as language and memory [64, 65]. Therefore, β rhythms may be of diagnostic importance in dementia, especially in its early stages [29, 33].

Other coupling measures and ROC curves have been used to distinguish MCI patients from controls. Bajo *et al.* [22] achieved values of area under the ROC curve between 0.72 and 0.82 for a MEG database composed by 22 subjects with MCI and 19 controls. In another MEG study [29], accuracy values of 69.8% were reached using *COH* and *SL*. Other authors implemented more complex classification approaches to help in MCI diagnosis. For instance, the use of linear and quadratic discriminant analysis, combining results from full-frequency directed transfer function (*DTF*) and stochastic event synchrony methods, yielded classification rates of 83% [24]. Lastly, Escudero *et al.* [25] distinguished MCI subjects from controls with an accuracy of 77.3% using stepwise logistic regression. It is important to note that all these results should be cautiously understood due to the use of different databases, usually with small sample sizes.

4.4. Limitations and future research lines

Several issues of this research merit further consideration. Firstly, the sample size is too small to prove the usefulness of our methodology as a diagnostic tool. For this reason, larger patient populations should be analyzed in the future. Secondly, connectivity values were grouped into eight pre-defined brain regions to facilitate the interpretation of the results, despite the loss of MEG spatial resolution. Future studies might benefit from exploring the affected regions in detail. Additionally, only two connectivity metrics (*COH* and *GC*) have been applied in this study to characterize the connectivity patterns in MCI, but several others (e.g. *SL*, *PLI*, *GFS*, *DTF*) might also provide valuable information about neuronal disturbances in this disorder. Finally, it is noteworthy that both *COH* and *GC* are influenced by volume conduction [66, 67], which can cause artificial synchrony between MEG channels.

However, we can assume that, in our study, volume conduction affects the connectivity estimations in a similar way for controls and MCI patients. Nevertheless, in order to mitigate this problem, future studies should estimate the connectivity at the source level or apply other measures that eliminate (or at least reduce) volume conduction effects, such as the imaginary part of *COH*, the phase-slope index or the transfer entropy [66–68].

4.5. Conclusions

This study investigated *COH* and *GC* of MEG signals in MCI patients. Our results suggested that MCI is associated with a widespread loss of functional and effective connectivity. However, significant differences between groups were found only with *GC*, mainly in the β frequency band. Moreover, *GC* provided a maximum accuracy of 79.54% to discriminate MCI patients from controls. Our results agree with previous studies that associated AD and MCI with a disconnection syndrome. This decrease in functional and effective connectivity exposes the cerebral histopathological abnormalities detected in these brain disorders.

ACKNOWLEDGEMENTS

This research was supported by 'Ministerio de Economía y Competitividad' and 'European Regional Development Fund' under project TEC2014-53196-R, by 'European Commission' and 'European Regional Development Fund' under project 'Análisis y correlación entre el genoma completo y la actividad cerebral para la ayuda en el diagnóstico de la enfermedad de Alzheimer' ('Cooperation Programme Interreg V-A Spain-Portugal POCTEP 2014-2020'), and by 'Consejería de Educación de la Junta de Castilla y León' under project VA037U16. Pablo Núñez was in receipt of a 'Promoción de empleo joven e implantación de la Garantía Juvenil en I+D+i' grant from 'Ministerio de Economía y Competitividad' and University of Valladolid.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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TABLES

Table 1. Socio-demographic and clinical data from MCI patients and healthy controls

	MCI patients	Controls
Number of subjects	18	26
Age (years) (mean ± SD)*	74.89 ± 5.57	71.77 ± 6.38
Gender (Female:Male)	10:8	17:9
MMSE (mean ± SD)*	25.67 ± 1.82	28.88 ± 1.18
FAST (mean ± SD)*	3.00 ± 0.00	1.73 ± 0.45

*SD = Standard deviation

FIGURE LEGENDS

Figure 1. Distribution of MEG channels into eight brain regions: left-anterior (dark orange), left-central (dark purple), left-lateral (dark blue), left-posterior (dark green), right-anterior (light orange), right-central (light purple), right-lateral (light blue), and right-posterior (light green). Midline MEG sensors were not used for our connectivity analyses. Examples of artifact-free epochs at different MEG channels from a control subject (blue) and a patient with MCI (red) are also displayed.

Figure 2. *COH* results for each frequency band. Left and central columns depict *COH* values for controls and MCI patients, respectively. Right column displays statistically significant values between groups, where connections between regions were only displayed when statistically significant within-group differences within groups were obtained (Mann-Whitney *U*-test, FDR-corrected p-values < 0.05). Red color tones indicate significant connectivity increases in MCI in comparison with controls, whereas blue color tones denote significant decreases.

Figure 3. *GC* results for each frequency band. Left and central columns depict *GC* values for controls and MCI patients (the arrows indicate the directionality of *GC* for a specific coupling between regions), respectively. Right column displays statistically significant values between groups, where connections between regions were only displayed when statistically significant within-group differences were obtained (Mann-Whitney *U*-test, FDR-corrected p-values < 0.05). Red color tones indicate significant connectivity increases in MCI in comparison with controls, whereas blue color tones denote significant decreases.