

Functional Connectivity in Mild Cognitive Impairment During a Memory Task: Implications for the Disconnection Hypothesis

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Abstract. Mild cognitive impairment (MCI) has been considered an intermediate state between healthy aging and dementia. The early damage in anatomical connectivity and progressive loss of synapses that characterize early Alzheimer's disease suggest that MCI could also be a disconnection syndrome. Here, we compare the degree of synchronization of brain signals recorded with magnetoencephalography from patients (22) with MCI with that of healthy controls (19) during a memory task. Synchronization Likelihood, an index based on the theory of nonlinear dynamical systems, was used to measure functional connectivity. During the memory task patients showed higher interhemispheric synchronization than healthy controls between left and right -anterior temporo-frontal regions (in all studied frequency bands) and in posterior regions in the γ band. On the other hand, the connectivity pattern from healthy controls indicated two clusters of higher synchronization, one among left temporal sensors and another one among central channels. Both of them were found in all frequency bands. In the γ band, controls showed higher Synchronization Likelihood values than MCI patients between central-posterior and frontal-posterior channels and a high synchronization in posterior regions. The inter-hemispheric increased synchronization values could reflect a compensatory mechanism for the lack of efficiency of the memory networks in MCI patients. Therefore, these connectivity profiles support only partially the idea of MCI as a disconnection syndrome, as patients showed increased long distance inter-hemispheric connections but a decrease in antero-posterior functional connectivity.

Keywords: Disconnection syndrome, functional connectivity, magnetoencephalography, memory, mild cognitive impairment, synchronization likelihood

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INTRODUCTION

The disruption of anatomic and functional connectivity in the brain of Alzheimer's disease (AD) patients due to neurofibrillary pathology [1] has led to the idea of conceptualizing the cognitive symptomatology as a disconnection syndrome [2]. This connectivity impairment suggests the existence of abnormal interactions between neuronal systems [3]. Because the pathophysiological characteristics of the disease seem to begin even decades before the cognitive symptomatology, it is of interest to evaluate whether functional connectivity profiles are affected in early clinical conditions such as Mild cognitive impairment (MCI), as patients suffering from MCI present a higher risk of developing dementia (rate of conversion of 10–15% per year [4]). Whether the early anatomical connectivity impairment modulates the profiles of functional connectivity in MCI patients is still a matter of debate [5].

To describe how brain regions are coordinated to support higher cognitive functions, the term functional connectivity has been coined ([6,7], see [8], for a classification of different types of brain connectivity). Functional connectivity reflects the statistical interdependencies between two physiological signals, providing information about functional interactions between the corresponding brain regions. Long range synchronization between signals (oscillatory activity) originated in relatively distant neuronal populations, has been proposed as the mechanism for communication and integration of information in the brain [9–11]. In fact, the binding phenomena in perception [12] or the formation of new memories [13] seems to be based on synchronization, at specific frequency bands, between two oscillatory time series which reflect activity from two brain regions.

Previous fMRI studies using functional connectivity in MCI patients have shown decreases [14–16] and increases in functional connectivity values [15,16] in MCI patients as compared with healthy age-matched participants. However, although fMRI connectivity measures provide spatially-resolved information about connectivity patterns between brain regions, they do not directly reflect coupling between neuronal oscillators in different frequency bands known to play distinct roles in cognition (see [17] for an example on MCI). For this purpose various connectivity measures for magnetoencephalography (MEG)/electroencephalography (EEG) have been developed [18–20], as MEG/EEG signals provide a direct measure of neuronal activity with high temporal resolution.

Here we use Synchronization Likelihood (SL) [21], an index which provides a nonlinear characterization of functional connectivity, to: 1) describe the synchronization topologies that support memory success in MCI patients and healthy aging participants and thus evaluate the disconnection hypothesis and 2) evaluate whether these synchronization topologies allow to differentiate between MCI and age matched elderly controls. Moreover, the rationale for using SL in this study is two-fold: First, SL has been widely used as a functional connectivity measure in AD patients with both EEG [22,23] and MEG [24]. Second, it is a robust and nonlinear algorithm which overcomes the limitations of linear approaches. SL could be complementary to other measures of functional connectivity such as mutual information and phase synchronization. More importantly, functional connectivity measures could add significant diagnostic information to other biomarkers such as anatomical connectivity or measures of amyloid- β ($A\beta$) deposition and neurofibrillary tangles that probably represent the origin of anatomical disconnection in AD. Disconnection in AD is associated with an increase in local synchronization [24]. The same finding in MCI would suggest that damage to anatomical connectivity already occurs at this stage. On the other hand, an increase in long distance synchronization would be compatible with the use of alternative networks.

MATERIALS AND METHODS

Participants

Forty-one right handed, elderly participants recruited from the Geriatric Unit of the Hospital Universitario San Carlos, Madrid, participated in the study. Participants were divided into two groups based on their clinical profiles: twenty-two participants were classified as multi-domain MCI patients, and the other nineteen as healthy control volunteers. Three MCI recordings were excluded from further analysis due to an excessive noise level.

MCI diagnosis was established according to the criteria proposed by Petersen ([4], see also [25]). To be diagnosed as having MCI, patients had to fulfill the following criteria: 1) report cognitive complaints corroborated by an informant (a person who stays with the patient for half a day at least 4 days a week); 2) objective cognitive impairment, documented by delayed recall as measured by the Logical Memory II subtest of the Wechsler Memory Scale Revised (score below 17

for 16 or more years of education; score below 9 for 8 to 15 years of education) and 1.5 Standard Deviations (SD) below mean in test of executive functions such as WCST or Stroop; 3) normal general cognitive function, as determined by the clinician's judgment based on a structured interview with the patient and an informant; 4) a MMSE score greater than 24; 5) relatively preserved daily living activities as measured by the Lawton scale; and 6) not sufficiently impaired, cognitively and functionally to meet criteria for dementia. As a result twenty-two participants were included in the MCI group. According to their clinical and neuropsychological profile, all participants in this group were considered multi-domain MCI patients [4]. Nineteen age-matched, healthy elderly volunteers, without memory complaints, recruited for a project called "Aging with Health", at the San Carlos Hospital in Madrid consented to participate in the study. This group undergoes a complete medical revision every year. Patients and controls underwent a neuropsychological assessment, in order to establish their cognitive status in multiple cognitive functions. Specifically, memory impairment was assessed by the Logical Memory (immediate and delayed) from the Wechsler Memory Scale-III-R. Two scales of cognitive and functional status were also applied: the Spanish version of the Mini Mental State Examination (MMSE) [26], and the Global Deterioration Scale/Functional Assessment Staging GDS/FAST [27]. In order to avoid possible differences due to the years of education, patients and controls were chosen so that the resulting average number of years of education was similar: 10 years for patients and 11 years for controls. Table 1 summarizes the demographic and clinical information for both groups. The fact that our sample of MCI patients came from a memory clinic rather than from a population based sample could explain the high proportion of amnesic multidomian MCI.

Before the MEG recording, all participants or legal representatives gave informed consent to participate in the study. The study was approved by the local ethics committee.

Stimuli and task

A modified version of the Sternberg's letter-probe task ([28,29]) was used. A set of five letters was presented and the participants were asked to keep the letters in mind. After the presentation of the five-letter set, a series of single letters (1000 ms in duration with a random ISI between 2–3 s) was presented one at a time, and the participants were asked to press a button

Table 1

	Age	MMSE	GDS	LM1	LM2
Control	71.6 ± 8	29.5 ± 0.7	1	42.5 ± 8*	26.7 ± 7*
MCI	74.8 ± 3	27.7 ± 1	3	19.1 ± 5	13.1 ± 6

MMSE, Mini-Mental State Examination; GDS, global deterioration scale; LM, logical memory.

* $p < 0.0001$ showing the differences in LM1 and LM2 between control and MCI cases.

with their right hand when a member of the previous set was detected. The list consisted of 250 letters in which half were targets (previously presented letters), and the remaining letters were distracters (different from the previously presented letters). All participants completed a training session before the actual test, which did not start until the participant demonstrated that he/she could remember the five-letter set. Letters were projected through a LCD video-projector (SONY VPL-X600E), situated outside of the shielded-room onto a series of in-room mirrors, the last of which was suspended approximately 1 meter above the participant's face. The letters subtended 1.8 and 3 degrees of horizontal and vertical visual angle respectively.

MEG data collection

The MEG signal was recorded with a 254 Hz sampling frequency and a band pass of 0.5 to 50 Hz, using a 148-channel whole-head magnetometer (MAGNES® 2500 WH, 4-D Neuroimaging) confined in a magnetically shielded room. An environmental noise reduction algorithm using reference channels at a distance from the MEG sensors was applied to the data. Thereafter, single trial epochs were visually inspected by an experienced investigator, and epochs containing visible blinks, eye movements or muscular artifacts were excluded from further analysis. Artifact-free epochs from each channel were then classified into four different categories, according to the subject's performance in the experiment: hits, false alarms, correct rejections, and omissions. Only hits were considered for further analysis because we were interested in evaluating the functional connectivity patterns which support recognition success. 35 epochs were used to calculate SL values. This lower bound was determined by the participant with least epochs. To have an equal number of epochs across participants, 35 epochs were randomly chosen from each of the other participants.

In the only previous SL-memory study we are aware of [30], a 1 minute time-window was used for SL analysis. Such a long time-window makes it difficult to ensure the homogeneity of the cognitive processes in-

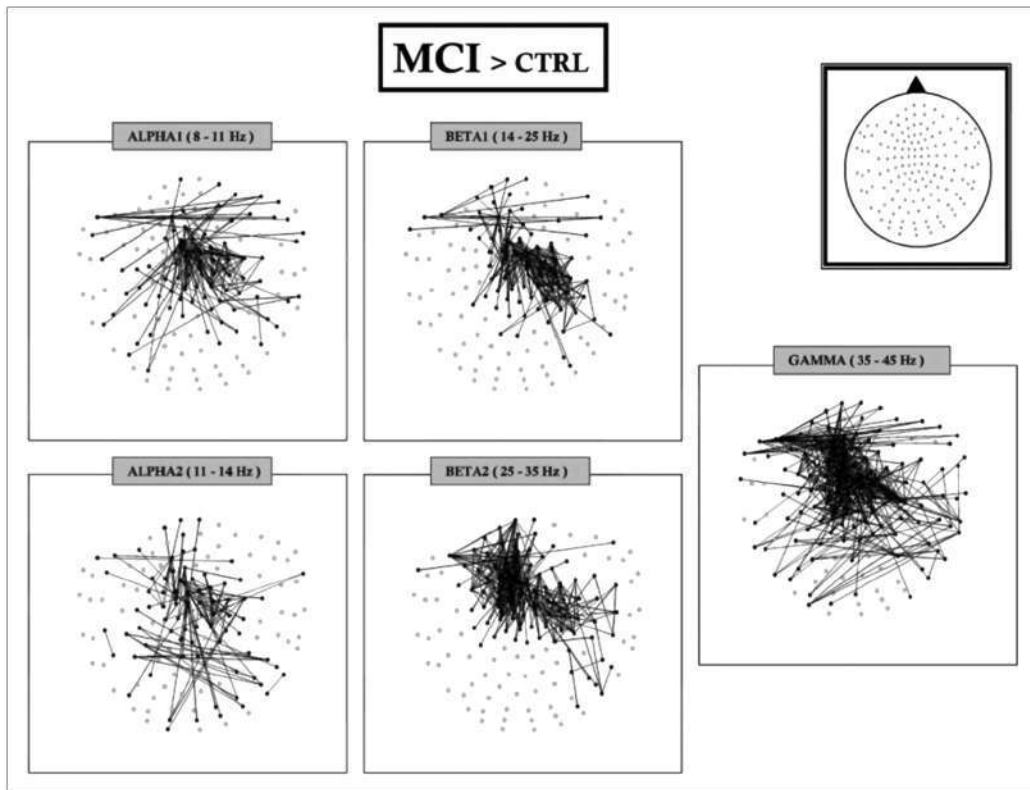


Fig. 1. Significant differences in SL between electrode pairs for different frequency bands. (MCI > Control). False Discovery Rate type I was applied.

volved. Thus, it seems convenient to apply the traditional SL algorithm to a shorter time window. This will lead to an Event Related-SL (ER-SL) that achieves the stability of functional connectivity patterns across participants during the memory task.

In-house Fortran code was used to implement the SL algorithm as described by [21]. The SL algorithm was applied to the 35 extracted artifact-free one second epochs for each subject. For each frequency band optimal SL parameter values were chosen according to [31] for each frequency band and one second length:

$$\text{Lag: } L = f_s / (3 * HF),$$

$$\text{Embedding dimension: } M = 3 * HF / LF,$$

$$\text{Theiler window: } W1 = 2 * L * (M-1), \text{ Pref below } 0.05,$$

$$\text{Window length: } W2 > 10/\text{Pref} + W1 - 1.$$

Where f_s sampling rate, and HF and LF are the high and low frequency bound, respectively.

The following frequency bands were considered: alpha1 (α_1 , 8–11 Hz), alpha2 (α_2 , 11–14 Hz), beta1 (β_1 , 14–25 Hz), beta2 (β_2 , 25–35 Hz), gamma (γ , 35–45 Hz). The SL index was not computed for bands

under 8 (Hz) as the epoch length and sampling rate do not allow an accurate enough estimation [31].

All epochs were digitally filtered off-line at the above frequency bands. Subsequently, the SL was calculated for each of the 35 one-second epochs with $148 * 147 / 2$ channel pairs for each frequency band, unfiltered epochs, and each subject (19 controls and 19 patients).

Statistical analysis

To compare the level of SL between the 2 groups, SL values were first averaged across epochs for each participant and channel pair. Then, False Discovery Rate [32, 33] was applied to find channel pairs with significant differences between groups. For each channel pair a between-groups Kruskal-Wallis (non-parametric) test was calculated. From the resulting p-values a significance threshold was calculated with a corresponding $q = 0.2$ ($q = 0.4$ in α band) using the type I false discovery rate implementation from [33].

Additionally, we analyzed similarities in the connectivity patterns of MCI patients and controls at the in-

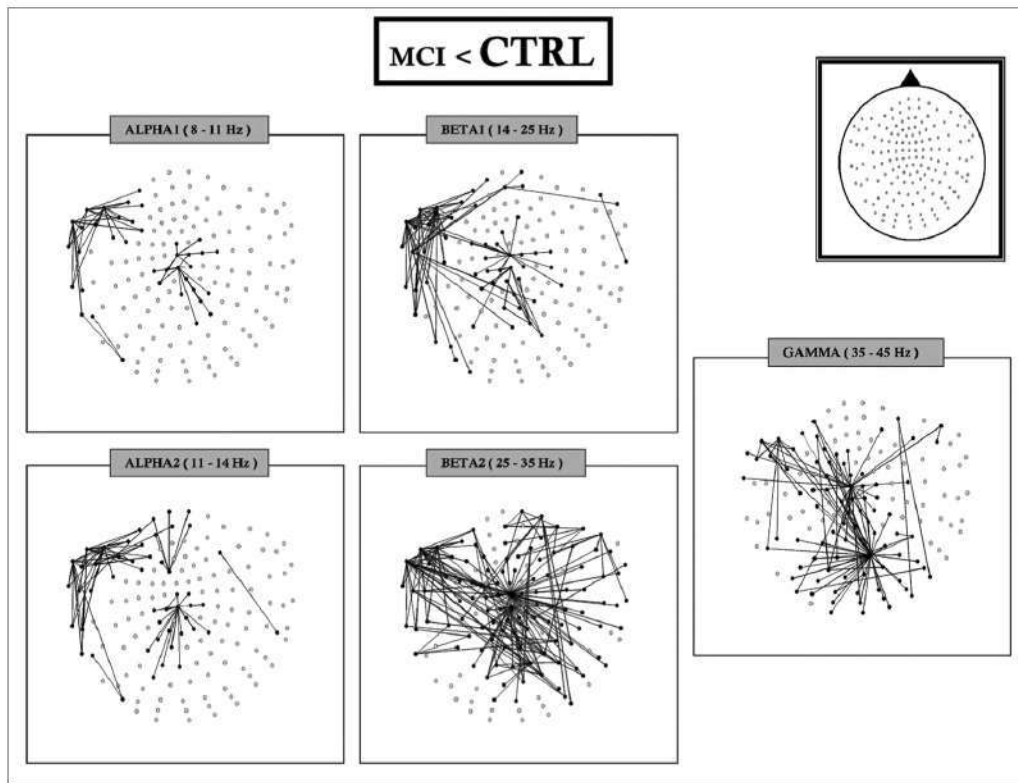


Fig. 2. Significant differences in SL between electrode pairs for different frequency bands. (MCI < Control). False Discovery Rate type I was applied.

dividual level. For each individual we report connectivity values 2 standard deviations above or below the average value across all channel pairs.

RESULTS

Behavioral performance

Behavioral performance during the memory task revealed no significant differences between groups, either with respect to the targets (total number of hits, misses and reaction time), or to the distracters (correct rejections, false alarms and reaction time). The percentage of hits (80% control group and 84% MCI group) and correct rejections (92% control group and 89% MCI group) was high enough in both groups, indicating that participants actively engaged in the task.

MEG profiles of functional connectivity

MCI > Control participants

Comparing both groups (see Fig. 1), MCI patients showed a clear cluster of higher synchronization values

over the anterior and central regions in all frequency bands. Additionally, MCI patients showed higher inter-hemispheric SL values than the control group between left and right temporo-frontal sensors in all frequency bands. Finally, only in γ band, MCI subjects present a pattern of higher inter-hemispheric SL than controls in posterior regions.

MCI < Control participants

Two non-functionally related clusters of local interactions showed higher SL values in the control group: one among left temporal sensors and another one in central-posterior channels. Both of them were found in all frequency bands. Additionally, controls showed higher SL values, in γ and $\beta 2$ bands, between central and posterior channels and between frontal and posterior regions. Finally, also in γ band, there is a higher posterior synchronization in controls when compared to patients (see Fig. 2).

Single-patient analysis: MCI and control participants

We calculated the average SL for each participant. SL values above and below two standard deviation from

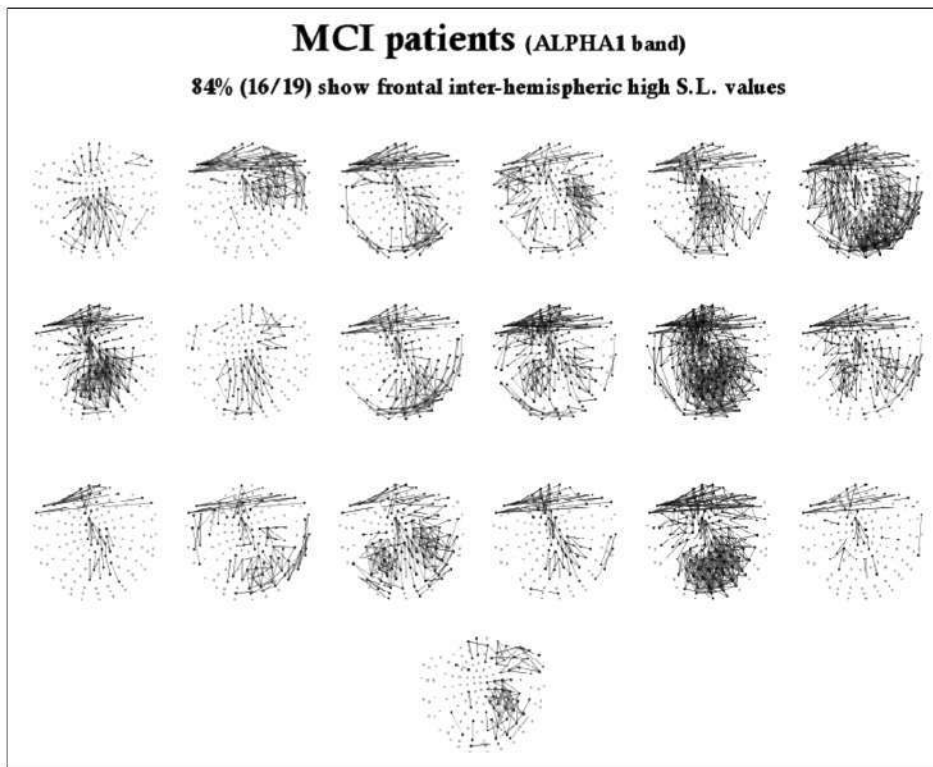


Fig. 3. SL for individual MCI patients ($N = 19$) in the α_1 band. Black lines indicate electrode pairs with SL two standard deviations above or below the individual SL average. 16 out of 19 patients show high frontal interhemispheric SL values.

the average are shown (Fig. 3). Profiles of synchronization in Fig. 3 resemble those of the between-group comparison (Figs 1 and 2). Although results for the α_1 band are shown they were similar for other frequency bands. MCI patients present a remarkable pattern of high inter-hemispheric SL values between left and right temporo-frontal sensors. In order to get a clearer figure, connections between nearest neighbours were not plotted. Most of the MCI patients (16/19) showed a high anterior inter-hemispheric SL in all frequency bands. In contrast, this pattern appears only in 7/19 control participants.

Receiver operating characteristic (ROC) curve

To assess the ability of SL to discriminate between MCI and control participants during successful memory encoding, we calculated the receiver operating characteristic (ROC) curve [34,35], which provides a graphical representation of the trade-off between sensitivity and specificity as a function of the classification threshold. We took the average SL across channel pairs showing significant differences between controls and patients as a classification variable.

Figure 4 shows the ROC curve for the mean SL across channel pairs where control $>$ MCI, for β and γ frequency bands. High values of area under the ROC curve (between 72% and 82%) were found, indicating that the connectivity patterns for the two groups were clearly different.

DISCUSSION

Our study is partly motivated by the question of whether MCI can be considered a disconnection syndrome. The results show a differential synchronization topography between MCI patients and controls. In general, while patients showed a tendency for higher inter-hemispheric synchronization among anterior sensors, controls showed a distinctive pattern with higher SL values over the left hemisphere and posterior regions, in addition to interconnections between fronto-posterior regions in β_2 and γ bands. The fact that controls and patients used different memory networks suggests that MCI patients were compensating for the inefficiency of the antero-posterior connections, in agreement with previous findings [36].

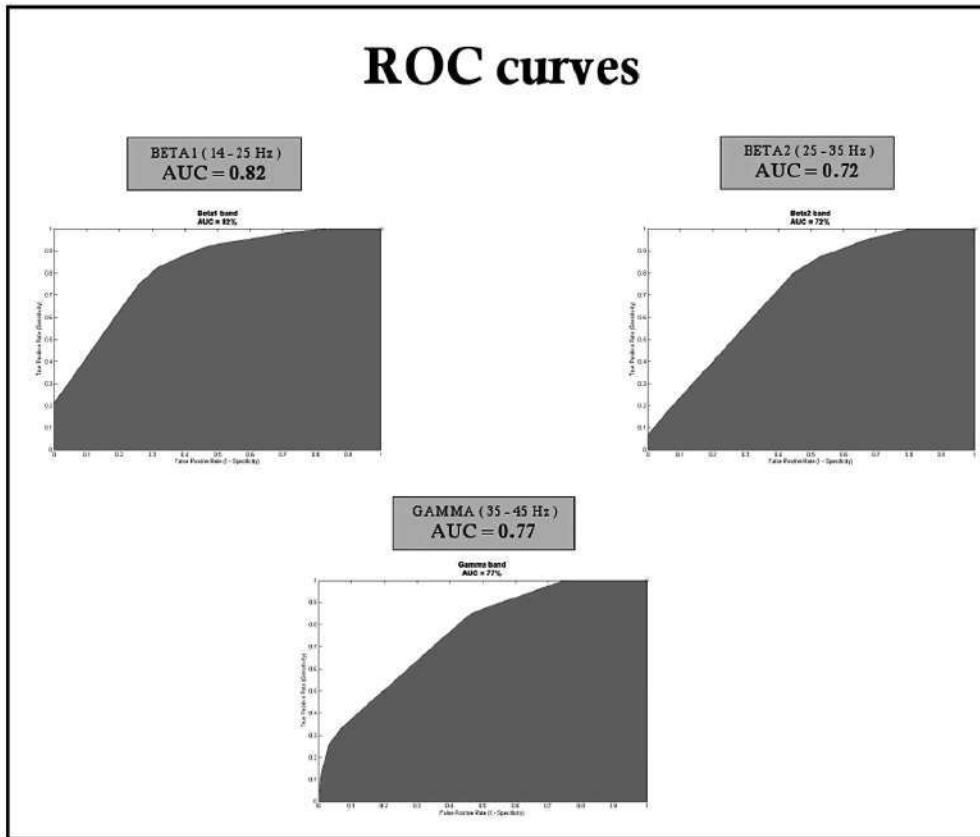


Fig. 4. Receiver Operating Characteristic for β and γ frequency bands. The variable used for classification was the average SL across sensor pairs with significantly higher values for controls as compared to patients. AUC=Area under the curve.

The higher inter-hemispheric synchronization in MCI patients among anterior regions was present in all frequency bands considered. It is of interest that, as we can see in figure 3, sixteen out of nineteen MCI patients showed anterior inter-hemispheric connectivity, which reflects the stability of the connectivity profiles across patients. Previous working memory EEG studies have shown increased inter-hemispheric coherence in MCI patients in the δ to β range [37–39]. The synchronization cluster over the central regions, also present in the MCI group, has been previously described in AD patients, although the AD group showed a more posterior pattern than our MCI patients see [24]. The increase in synchronization in certain areas in patients may be the result of a loss of functional interactions in other regions. An example of increased synchronization by disconnection has been demonstrated by pharmacological isolation of one hemisphere by amobarbital injection, which induces an increase of β band synchronization over the non-injected hemisphere [40]. Thus, an impairment of certain brain networks can induce an in-

crease in synchronization in other networks, probably reflecting a compensation mechanism. A pattern of higher synchronization in MCI patients has been described previously in the only EEG study that calculated the SL during a memory task [30]. These authors found higher short-distance α band (8–10Hz) SL values for the MCI group as compared to a group of elderly participants with subjective memory complaints. By contrast, in our study we found long distance synchronization in several frequency bands in comparison to a group of healthy controls without memory complaints. The fact that we were evaluating only hit responses and the use of a working memory instead of an episodic memory task could be a source of differences between studies.

In all frequency bands, controls showed higher SL values over the left hemisphere, particularly among left temporal sensors. The fact that participants were all right handed and were performing a verbal memory task, may explain the involvement of left temporal regions. It has been recently suggested that the functional

coupling of α rhythms could constitute a neural substrate for language lateralization [41]. The increased synchronization in controls may reflect a more efficient processing of verbal stimuli.

Differences between groups in the γ band were of great interest. In addition to the main differences found in the other bands, MCI patients showed an increase in posterior inter-hemispheric connectivity while controls showed long distance interconnection between frontal and posterior regions accompanied by a posterior synchronization cluster. Differences in this band have not been frequently reported in EEG studies (see [42] for a recent example; see [43] for a γ study). This difference between EEG and MEG might be ascribed to a better signal to noise ratio in high frequency bands in MEG as compared to EEG, as biological tissue is much more transparent to magnetic fields than to electrical potentials, making MEG more sensitive to γ band effects. It has been proposed that the γ band plays an important role in high cognitive processing such as in the integration of information [44] or in attention [45]. In fact, Kaiser et al. [46] propose that γ band modulations reflect the synchronization of sub-processes in neuronal networks related to cognition. Several studies have related γ activity to memory processes [47]. Specifically, cross-frequency coupling between the γ and θ bands in the medial temporal lobe is a predictor of memory performance [48,49].

An interaction between frontal and parietal regions during working memory tasks can be expected, as revealed by lesions in animals and humans and by functional neuroimaging studies [50]. Furthermore, functional dependencies between frontal and posterior areas have been previously associated with memory formation and recovery [49]. Thus, the pattern of long distance SL in the γ band found in the control group could reflect a fronto-posterior interaction associated with the working memory task. Higher connectivity in healthy elders than AD patients between these areas has been previously reported [23]. In our study, MCI patients may rely less on the fronto-posterior connection to perform the task and more on alternative networks. Thus, the pattern of increased inter-hemispheric connectivity in MCI may represent a transitory physiological state as MEG and EEG studies of functional connectivity in AD patients showed a decrease in γ band synchronization [43,51].

Since only hit responses were included in our analysis we cannot conclude that differences in synchronization profiles imply that patients use a less efficient network. In fact, α - and β -synchronization have been

related to successful performance in short-term memory tasks [52,48]. Thus, between groups profile differences of SL could indicate that control and patients were using a different cognitive strategy to perform the task.

In general, the increased inter-hemispheric synchronization in MCI patients could be interpreted as a compensatory mechanism. In fact, our results seem to agree with the Hemispheric Asymmetry Reduction in Older adults (HAROLD) model. The HAROLD model states that, under similar circumstances, prefrontal activity during cognitive performance tends to be less lateralized in older than in younger adults [53]. Thus, according to this model, older adults recruit right hemisphere frontal regions to compensate for the loss of efficiency of the left hemisphere networks. This compensatory mechanism found in aging seems to be exhaustively used by the MCI patients, suggesting that they recruit more often right hemisphere regions to perform the verbal task. Similarly, when the complexity of the task increases, young participants tend to recruit right hemisphere regions during the performance of verbal tasks [54]. Thus, it could be hypothesized that the increase in inter-hemispheric synchronization in MCI patients reflects the recruitment of right hemisphere areas to compensate for: 1) the loss of efficiency of the left hemisphere verbal memory networks and 2) the reduced synchronization of the fronto-posterior networks.

Functional connectivity fMRI studies in MCI patients showed higher connectivity values within the posterior regions [15,16]. Here we show that this pattern of posterior interactions is extended to the anterior regions of the brain. Differences between studies could be due to the type of analysis performed in each study (frequency domain versus blood flow) [55] and the type of responses considered in each of them as in the fMRI studies "hits" were not always considered separately from other types of responses.

We hypothesized that the increase of synchronization in MCI patients could be interpreted as a compensatory strategy for the loss of cognitive efficiency of the memory networks that are normally activated in healthy age-matched subjects. Previous functional neuroimaging and physiological studies have described other possible signs of this compensatory process such as the increase in activity in the medial temporal lobe [56] or the plasticity of the cholinergic system [57]. This finding opens the possibility to neuropsychological interventions benefitting from the existence of spared cortical networks related to memory success in MCI pa-

tients. Additionally, the patterns of synchronization topography found in this study reveal a tendency to use differential memory networks in each group to achieve similar task performance. This is probably due to the use of different recognition strategies in each group.

It could be argued that the inter-hemispheric patterns of functional connectivity found in MCI patients are not compatible with the reported damage in white matter found in this group of patients [58]. Nevertheless, MCI patients show loss of axons but not demyelination. Thus, while AD patients show more extensive damage to white matter [59], MCI patients demonstrate an anatomical connectivity that is better preserved, opening the possibility for long distance communication [60]. These findings do not argue against the notion of AD as a disconnection syndrome. Rather, our data suggest that during MCI the brain is still able to compensate for potential initial anatomical defects resulting in an increase of functional connectivity, before AD developments.

In conclusion, the fact that MCI patients are able to establish long distance connections argues against the disconnection hypothesis in this neurological condition. This higher anterior interhemispheric synchronization profile showed by the MCI group could reflect the use of a different cognitive strategy to solve the task because: 1) controls used an anterior-posterior profile of connectivity and 2) profiles of connectivity were obtained for hit trials when processing has been efficient. Thus, the lack of observed disconnection syndrome is due to an apparent compensatory mechanism in MCI subjects. The existence of anterior interhemispheric synchronization could be related to the fact that our sample is formed by amnesic-multidomain MCI. Since in the majority of the cases memory dysfunction was accompanied by executive impairment, the deficit in frontal lobe cognitive abilities would lead to increased compensatory interhemispheric synchronization over this brain region. In fact, there is an increasing evidence of a compensatory response in MCI and early AD see [61] and there are certainly models related to this issue [62,63].

The fact that our sample of MCI subjects was formed essentially by amnesic multidomain MCI subjects (which is associated a more severe state than single domain amnesic MCI) could explain the more prominent difference between MCI subjects and controls. Future studies should evaluate the ability of MEG and SL to differentiate between single domain amnesic MCI subjects and controls. Moreover, the fact that there were clear differences between groups indicates that

MEG derived connectivity measures could contribute to the diagnosis of MCI. Future studies should evaluate whether this SL profiles are useful in predicting which of the MCI patients will develop dementia.

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