Dysfunctional and compensatory duality in mild cognitive impairment during a continuous recognition memory task

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Abstract

One of the current issues of debate in the study of mild cognitive impairment (MCI) is deviations of oscillatory brain responses from normal brain states and its dynamics. This work aims to characterize the differences of power in brain oscillations during the execution of a recognition memory task in MCI subjects in comparison with elderly controls. Magnetoencephalographic (MEG) signals were recorded during a continuous recognition memory task performance. Oscillatory brain activity during the recognition phase of the task was analyzed by wavelet transform in the source space by means of minimum norm algorithm. Both groups obtained a 77% hit ratio. In comparison with healthy controls, MCI subjects showed increased theta ($p<0.001$), lower beta reduction ($p<0.001$) and decreased alpha and gamma power ($p<0.002$ and $p<0.001$ respectively) in frontal, temporal and parietal areas during early and late latencies. Our results point towards a dual pattern of activity (increase and decrease) which is indicative of MCI and specific to certain time windows, frequency bands and brain regions. These results could represent two neurophysiological sides of MCI. Characterizing these opposing processes may contribute to the understanding of the disorder.

Keywords: Mild Cognitive Impairment (MCI), Magnetoencephalography (MEG), Memory, Time-Frequency analysis and Source space.

1. Introduction

Mild cognitive impairment (MCI) has been considered as a major precursor of Alzheimer's disease (AD). Evidence suggests that the conversion rate from MCI to dementia is of about 12% per year, while healthy controls convert at a 1–2% rate, and that MCI show a clear cognitive profile and neuropathological signs of AD (Petersen, 2004; Petersen et al., 2001, 2006; [see Twamley et al., (2006) for a review of neuropsychological and neuroimaging literature on preclinical AD]). Thus, early identification of patients at risk for the development of dementia, such as MCI population, might be crucial for providing them cognitive and/or pharmacological interventions to slow down the progression of cognitive deficits and retard the onset of disability.

It has been consistently demonstrated that brain oscillations underlie human information processing and fundamental aspects of cognition (Buzsaki, 2006). Since memory processes have been shown to be related to oscillations in the theta, alpha, beta, and gamma frequency ranges (Klimesch, 1999; Tallon-Baudry et al., 1999; Jensen and Tesche, 2002b; Leiberg et al., 2006), spectral changes during such tasks are good candidates to study memory related pathologies.

Memory loss is the most common clinical symptom of MCI and AD (Baddeley, 1991; Belleville et al., 1996; Lautier et al., 2007; Caza and Belleville, 2008). fMRI studies have extensively shown brain activity increases in MCI when comparing with controls (Clement and Belleville, 2010; for a review see Dickerson and Sperling, 2008). Although the majority of the MEG and EEG studies in AD and MCI have focused on resting state recordings, the dynamics of the neuronal electromagnetic activity during a memory task could provide more reliable information to study cognitive consequences of pathological aging (Van der Hiele et al., 2007a; Giannakopoulos et al., 2009). In this

line, EEG and MEG studies of modified versions of the Sternberg letter-probe task (De Toledo-Morrell et al., 1991) have been able to address patterns of brain activity specific to MCI pathology (Maestu et al., 2008; Hogan et al., 2003; Bajo et al., 2010). These studies are based on event related field source reconstruction analysis and on fast-fourier transform, time-frequency and connectivity analysis in sensor space, respectively. Therefore, the study of the time-frequency MEG dynamics in source space during the recognition stage of a memory task has not been addressed yet in MCI patients (see below the main statements of the present study). Two previous studies evaluated time-frequency activity in MCI patients using the Sternberg paradigm (Kurimoto et al, 2012; Karrasch et al, 2006). These studies analysed the encoding and/or maintenance stages of the task. Only one of them found differences between controls and MCIs and these differences were found in the sensor space. Thus, it seems necessary a study evaluating: 1) time-frequency power; 2) at the source space; 3) at the recognition stage of a memory task.

Electroencephalographic brain activity increases and decreases have been variably reported in the characterization of MCI (Grunwald et al., 2002; Jiang, 2005; Missonnier et al., 2006a; Van der Hiele et al., 2007a,b; Zheng et al., 2007; Cummins et al., 2008; Deiber et al., 2009). In this line, fMRI literature of cognitive aging postulates that activity increases are associated with neural compensation by means of additional recruitment of neurons in order to prevent performance decreases (Cabeza et al., 2002b; Dickerson et al, 2005; Grady et al., 2005). On the contrary, activity decreases have been related to brain dysfunction associated with neuronal loss as a degenerative process causing performance decrease (Friston and Price; 2003; Scarmeas et al., 2003; Johnson et al., 2006). Overall, activity decreases may be a precursor of AD and would need a follow-up for verification. Thus, the variety of results reported so far could reflect

pathological compensatory and dysfunctional processes acting simultaneously in the altered brain (Clément and Belleville, 2010).

In order to study task-related brain dynamics of MCI, we report brain spatial-time-frequency differences between MCI patients and controls during a continuous recognition memory task based on the following statements: 1) the data will be recorded during the execution of a memory task because differences between groups will be highlighted (Vander Hiele et al., 2007a); 2) data will be acquired with MEG due to its high temporal resolution; 3) a time-frequency analysis (with a wavelet transform approach) will be applied and offer the opportunity to study differential dynamics of the activity across the frequency spectrum; 4) data will be analyzed in the source space, which will provide an accurate information about the brain regions involved; 5) the patterns observed in the control group will be the gold standard pattern of activation. Thus, any deviation in brain activity from controls (both hyper and hypoactivation) will be considered pathological.

Compensatory activity will be considered when a particular profile of activation (increasing or decreasing respect to the control group) demonstrates an improvement in cognitive function (i.e. positive correlation between increased activation at a certain frequency band and performance on memory test). Dysfunctional activity will be considered when an activity pattern deviates from the control group without any sign of improving cognitive function. This analysis will offer a further step in the knowledge of the brain dynamics underlying MCI, and will allow us to evaluate the compensatory and dysfunctional hypothesis.

2. Materials and Methods

2.1. Subjects

Twenty- five age matched elderly subjects (see table1) participated in the study. Participants were divided into two groups based on their clinical profiles: 12 were diagnosed with amnesic MCI and 13 were considered as elderly healthy control subjects. Patients were recruited from the Geriatric Unit of the University Hospital San Carlos (Madrid, Spain), whereas controls were recruited from a day care centre. To avoid potential sources of differences due to handedness and its relation with hemispheric dominance that could affect the organization of brain activity, we decided to keep this variable stable across subjects (see Long et al 2012). Thus, participants (patients and controls) were all right handed (> 40 in the Oldfield's Edinburgh Handedness Inventory (Oldfield, 1971); following the formula $R = (D / CT) \times 100$; where D is right handed (RH) - left handed (LH) and CT is LH + RH).

MCI diagnosis was established according to the criteria proposed by Petersen (2004). Thus, MCI patients fulfilled the following criteria: (1) cognitive complaint corroborated by an informant (a person who stays with the patient for half a day almost 4 days a week); (2) objective cognitive impairment, documented by delayed recall from the Logical Memory II subtest of the Wechsler Memory Scale Revised (cut-off scores ≤ 16 for ≥16 years of education; ≤8 for ≥8–15 years of education) (MCI's scores: Logical Memory I (LM-I)=10.3±3.9; Logical Memory-II (LM-II)=3±3.5); (3) normal general cognitive function, as determined by clinician's judgment based on a structured interview with the patient and an informant. Additionally a MMSE score greater than 24; (4) preserved daily living activities (assessed with the Spanish version of the Functional Assessment Scale [Pfeffer, 1982]); (5) not sufficiently impaired, cognitively and functionally to meet criteria for dementia. According to their clinical and neuropsychological profile all subjects in this group were considered amnesic MCI.

The healthy control group was selected according to a neuropsychological assessment and based on the demographic characteristics of the experimental group. Exclusion criteria for the selection of all participants included (1) previous medical history of psychiatric or any other neurological disease; (2) psychoactive drugs consumption and (3) severe sensory or comprehension deficits. Before the MEG recording, all participants or legal representatives signed an informed consent that explains the technical and ethical considerations of the technique. The Local Ethics Committee had approved the study.

Table1.

2.2. Stimuli and task

MEG scans were obtained in the context of a modified version of the Sternberg's letter-probe task (De Toledo-Morrell et al., 1991; Maestú et al., 2001). During the task a set of five letters was presented simultaneously for 30 seconds and the subjects were asked to keep the letters in mind (encoding phase). After the presentation of the five-letter set, a series of single letters (500 ms in duration with a random interval between 2 and 3s) was introduced one at a time, and the participants were asked to press a button with their right hand when a letter of the previous set was detected (recognition phase). The list consisted of 250 letters. Half of them were targets (previously presented letters), and the remaining letters were distractors (not previously presented letters). All of the subjects practiced a training series before the real test, and the single letter presentation did not start until the participant demonstrated that she/he remembered the five-letter set. Letters were projected by an LCD video-projector (SONY VPL-X600E) located outside the magnetically shielded-room onto a series of in-room mirrors, the last of which was suspended approximately 1m above the subject's face. The letters subtended 1.8º and 3º of the horizontal and vertical visual angle, respectively.

2.3. MEG data collection

The MEG signal was recorded using a 148-channel whole-head magnetometer (MAGNES ® 2500, 4-D Neuroimaging Inc., San Diego, CA, United States) situated in a magnetically shielded room (see Figure1 for schematic illustration of experimental and analysis protocol). The sampling rate was 254.31 Hz. The signal was filtered online with a band pass filter between 0.1 and 50 Hz. Then, the data were submitted to a noise reduction procedure, which uses simultaneous recordings from nine gradiometer reference channels that are part of the MEG system. Due to a high percentage of correct responses (77% of hits, correct responses, in both groups) and to a low percentage of errors (10% of errors in the control group and 15% of errors in the MCI group), our analysis was based on the recognition phase of the target stimuli to ensure equal signal to noise ratios across groups. Epochs (composed of 3000 ms; from 1500 ms before to 1500 ms after the stimulus onset) contaminated by ocular artefacts were corrected by means of BESA artefact-correction tool (Brain Electrical Source Analysis). Trials containing muscular artefacts were discarded from analysis. Overall, a minimum of 80 artefact-free epochs (64%) was entered the analysis.

2.4. Wavelet spectrum and source estimation

Time-frequency (TF) representation of MEG data was calculated on a single trial basis for a 3000 ms time window. Data was based on the wavelet transform of the signals (Tallon-Baudry et al., 1997; Mallat, 1998) using a Morlet wavelet function with a width of 5 cycles per wavelet in a spectral range between 2 and 88 Hz, in 1 Hz steps. Wavelet transform is a dynamical alternative to Fourier, used to perform time spectral analyses for non-stationary time series. The continuous wavelet transform (WT) of a signal suppose its projection onto a set of basic functions obtained from mother wavelet by rescaling and translating it along the time axis. Wavelet coefficients of the signal in the

time-spectral plane were obtained. TF representation was estimated using custom-written scripts in MATLAB Version 7.4 (Mathworks, Natick, MA).

Before estimating the cortical generators of the power changes at different latencies and frequency bands, the head sensor positions of each subject were spatially aligned (co-registered) with a surface brain model (3003 surface dipoles). The dipole mesh (representing sulci and gyri) was derived from a Collin 27 template brain aligned with the Montreal Neurological Institute (MNI) phantom brain as implemented in the Fieldtrip software package (http://www.ru.nl/fcdonders/fieldtrip/) (Collins et al., 1998). Thereby, in a first step the template brain's fiducials and the individually digitized fiducials were realigned. In a second step, subject specific digitized head shape points were fitted to the template scalp surface by minimizing the mean distance between the individual head shape points and the template scalp surface. After the co-registration of the MEG and phantom brain coordinate systems, the forward solution was calculated to determine the lead field matrix for further source inversion, using a head model based on overlapping spheres. For each channel a local sphere was fitted to the underlying head shape points (Huang et al., 1999).

The minimum-norm estimation procedure (MNE) was used to perform the source localization of the TF MEG signals. The underlying generator sources were estimated from wavelet coefficients (by combining the source projected real and imaginary parts) using the Fieldtrip software package (http://www.ru.nl/fcdonders/fieldtrip/) and custom-written scripts. Jensen and Vanni (2002c) demonstrated that by transforming the real and imaginary parts of the Fourier components in the source domain by means of MNE, it is possible to identify source areas of rhythmic activity in the frequency domain. Source representation of the time-frequency data was constructed by means of an L2 MNE procedure in the frequency domain, with a standard Tikhonov regularization to

control the noise of the data (Bouhamidi and Jbilou, 2007). Accordingly, in our study the underlying current source density (the source strength at each node of the MNI phantom brain) of four frequency bands (theta 4–8 Hz; alpha, 8–12 Hz; beta, 13–30 Hz; gamma, 30–45 Hz) was estimated (Jensen and Vanni, 2002c; Moratti et al., 2008). Note that the subdivision of the frequency bands in sub-bands (i.e. low/ high alpha and beta bands) can offer information about specific cognitive processes such as attention, task specific or motor related processes (Neuper and Pfurtscheller, 2001; Klimesch et al., 1998). However, an analysis of the sub-bands did not reveal differences when considering high and low alpha or beta bands separately. Therefore, we decided to maintain the classic divisions of the frequency bands in order to offer a holistic characterization of the spectrum between healthy controls and patients.

For the estimation of the underlying current source density, the real and imaginary parts of each wavelet component averaged within each of the four frequency bands was submitted to the MNE analysis. Thereafter, the MNE of the real and imaginary parts were combined by using the root square of the sum of squares of the two wavelet parts as an estimate of absolute amplitude. The change in amplitude was calculated with respect to a baseline period before the beginning of each epoch. For each frequency band, the mean time–frequency amplitude of the prestimulus period (between 1000 and 0ms before stimulus onset) was considered as a baseline and subtracted from the time–frequency representation in order to normalize it. Finally, data were log-transformed in order to reduce the effect of the non-Gaussian distribution (Pivik et al., 1993). As MEG is more sensitive to tangential sources with respect to the scalp surface, source activity is often localized within the sulci of the neo-cortex. For better visibility of this activity, MNE results are shown on a smoothed MNI brain surface.

Figure1.

2.5. Statistical Analysis

Before the estimation of the source activity, a control analysis was performed to test possible baseline differences between groups. Results showed no significant differences between groups at baseline (all comparisons show $p>0.05$), which indicates that differences observed in the post-stimulus interval are not influenced by differences in baseline.

A baseline corrected segment of 1000 ms after target stimulus onset was considered for statistical analysis. Source activity in the time-frequency domain was averaged over 26 time-windows of 39 ms each. Power values of each participant and at each dipole location of the brain surface mesh were statistically analyzed by using a Kruskall Wallis test to compare the spatial-time-frequency patterns between the patient and the healthy control group. Associated p-values were thresholded at $p<0.002$ (uncorrected) (see Gurtubay et al., 2001; Brookes et al., 2005; Osipova et al., 2005; Stam et al., 2006; Maestu et al., 2008; for a similar statistical approach). In addition, in order to reinforce the robustness of the results, a clustering analysis was applied (at least 2 neighbour brain sources or time points had to be significant at a p level of 0.002). The spatial and temporal clustering required, enhances the consistency of the data and strengthens its cohesion by avoiding spurious spatial changes in isolated sources and spurious dynamical fluctuations across time. Further post-hoc analysis were performed to explore whether age, task performance and/or neuropsychological test scores of MCI and control subjects were related to the power changes at statistically significant source clusters and time windows (according to the previously calculated statistical differences between groups per frequency band). Subsequently, Spearman's correlation coefficients were calculated with a cut-off of $p <0.03$.

3. Results

3.1. Behavioural performance.

Behavioural performance during the continuous recognition memory task showed: hits (77%), errors (8%) and correct rejections (92%) in the control group. Performance in the MCI group was as follows: hits (77%), errors (12%) and correct rejections (85%). These results revealed no significant differences between groups, neither with respect to the number of hits [$t(23)=0.007$, $p=0.994$], nor to the number of errors [$t(23)=0.584$; $p=0.565$] or correct [$t(23)=1.025$, $p=0.316$] rejections. The percentage of hits (77% for the control group and 77% for the MCI group) and correct rejections (92% control group and 85% MCI group) was high enough in both groups to indicate that all participants were committed to the task. Reaction times did not show significant differences between groups [$t(23)=0.871$, $p=0.395$].

3.2. Spectral power dynamics in source space.

Time-Frequency source representation for target stimuli was compared between MCI and healthy control participants. Statistical differences between MCI subjects and controls are summarized below (Figure2).

Theta spectral band. Compared to healthy controls, MCI patients showed higher induced theta power during the recognition phase in the right frontal pole ($p<0.001$) between 99-294 ms.

Alpha spectral band. However, between 489 and 528 ms after stimulus onset, MCI subjects were characterized by lower alpha power values in right temporo-occipital cortex ($p<0.002$).

Beta spectral band. Differences in beta power were localized in bilateral posterior parietal cortex and in parieto-temporal, frontal lateral and temporal posterior superior areas of the right hemisphere between 645-801 ms ($p<0.001$). The results indicate higher power values for the MCI group in comparison with healthy controls.

Gamma spectral band. Compared to controls, MCI patients demonstrated lower gamma power in left posterior parietal cortex between 372-411 ms ($p<0.001$) and 450-489 ms. Figure2.

3.3. Correlation analysis

Post-hoc analysis of the statistical differences in power and age, task performance and test scores between groups revealed linear relationships between theta oscillations and LM-I (Logical Memory I) subtest ($r=0.692$, $p<0.03$) for MCI subjects (see Figure4). Figure3.

4. Discussion

This study aimed at characterizing brain oscillatory power profiles of MCI patients, compared with healthy controls, at cortical source level during a continuous recognition memory task. Our neurophysiological results showed higher theta power in the right frontal pole and less beta power reduction in right prefrontal, temporoparietal and posterior parietal areas in MCI subjects compared to controls. However, MCI patients were also characterized by reduced alpha power in right temporo-occipital area and less gamma band power in left parietal posterior brain regions. The positive correlation obtained between theta oscillatory activity and performance on the memory test, while others did not achieve any correlation and/or showed a diminution of activity in comparison with the control group, leads us to suggest the presence of a brain duality pattern in the MCI brain. The fact that both groups achieved a high percentage of hits indicates an adequate sustained attention while performing the task and allows us to compare data more readily. Present findings offer a new perspective about the features and changes of a MCI brain, and contribute to the knowledge of the continuum to AD. Our results, in addition to previous literature, point out the capacity of current modified

Sternberg task to generate specific brain activity patterns which help to differentiate between clinical profiles.

The group with MCI showed an increase in theta power over the right frontal pole at early latencies (99-294) in comparison to the control group. The fact that this increased activity achieved a positive correlation with the performance on memory test (see Figure3) allowed us to interpret this activity as compensatory due to its relation with an improvement in the recall of information. Thus, cognitively more preserved MCIs (those who obtained higher scores in the LM-I subtest) were those who showed higher theta relative power compared to controls, and *vice versa*, suggesting a possible relationship between theta power and cognitive status in MCI subjects. Classical studies with EEG (Klimesch, 1996) demonstrate that during memory tasks theta activity tends to increase and correlate with performance. In fact, the coupling in theta between different regions of the medial temporal lobe has been correlated with improving performance on memory task (Fell et al., 2003; Axmacher et al., 2010). Furthermore, in line with our study Finnigan et al., (2011) observed positive correlations between theta and cognitive performance, and during haptic tasks, theta power increases have been suitable measures to distinguish healthy subjects from subjects with MCI and mild dementia (Grunwald et al., 2002). In a similar manner, fMRI studies show higher brain acitivity in MCI participants that in helathy controls during memory tasks (Bokde et al., 2010), which tends to reduce when the memory load increases (Kochan et al., 2011).

Present interpretation of theta activity in MCI patients as compensatory seems to be contradictory with the correlation found in previous studies between the increasing power of the theta and the cognitive impairment in AD and MCI patients (Coben et al, 1985; Prichep et al, 1994, 2006; Jelic et al, 1996, 2000; Grunwald et al, 2007; Moretti et al, 2009). However, these studies analyze brain activity during resting state conditions.

Thus, in addition to the difficulty to compare differences of power along the frequency bands and in different conditions (resting state versus memory task), it is important to point that these two conditions could even show results in opposite directions [see Bajo et al., (2010) and Gomez et al (2010)].

In studies were the oscillatory activity was recorded with EEG during the performance of a memory task, theta activity has shown a compatible profile of activity with that found in the current study. In this sense, during two n-back studies Missonier et al, (2006a) and Deiber et al., (2009) showed a decreased theta induced and event related synchronization (ERS) in progressive MCI (PMCI) but not in stable MCI (SMCI). The fact that in these studies the decrease of power in theta band increases the likelihood of progression to dementia, and that MCI patients who did not show the reduction were those who did not progress to dementia, reinforces the idea of linking the increased theta power with compensatory processes. Regarding the localization of the theta differences over the frontal lobe, it is interesting to point that the link between frontal theta activity and attentional processes has been consistently reported (Demiralp et al., 1994; Ishii et al., 1999; Aftanas and Golocheikine, 2001). Furthermore, its dependency on the attention level required has been established (Missonnier et al., 2006b; Deiber et al., 2007). These findings, together with the high task performance obtained during the recording, suggest the possible role of higher theta in increasing the level of attention towards target stimuli that enables MCI patients to compensate for the cognitive decline. The fact that theta hyperactivation in MCI patients is concentrated within the right hemisphere indicates the necessity to recruit additional areas over the non-dominant hemisphere during a verbal task in right-handed subjects. This effect has been described previously as a compensatory mechanism in healthy elders, performing a

verbal memory task, and has been referred to as the so-called HAROLD model (Hemispheric Asymmetry Reduction in Older adults; [Cabeza, 2002a]).

Through these data, we have been able to detect an additional effort of the MCI group in the form of increased theta power which probably contributes to achieve similar level of performance than the control group [see Dickerson et al, (2005) for similar interpretation with fMRI data].

Another frequency band which showed between group differences was in the range of the beta band. MCI subjects showed lower beta band power reduction, respect to the baseline and compared to controls, in right fronto-parietal regions at late latencies (between 645-801 ms). Beta band desynchronization in healthy elderly has been reported during the execution of the Sternberg paradigm at the recognition stage and thus, has been considered one of the neural mechanisms necessary to perform short-term memory tasks (Karrasch et al., 2004; Krause et al., 2007). Beta band profile of activity found in the present study did not correlate with memory test performance and consequently, we are not able to interpret this finding as a compensatory mechanism. In fact and in line with our results, a recent paper by Kurimoto et al (2011) using the Sternberg paradigm with AD patients showed lower beta event related desynchronization over the right hemisphere and interpreted this finding as a dysfunctional mechanism due to the fail of the memory networks to desynchronize in beta band.

Regarding alpha power in the present study, in comparison with the control group, it was reduced in the temporo-occipital region of the right hemisphere between 489-528 ms. Alpha band activity has been related with an active memory process during memory tasks (Palva and Palva, 2007). In fact, increases in both power and functional connectivity measures have been observed as a function of memory load or during

working memory (Jensen et al, 2002a; Palva et al, 2010; Van Dijk H et al, 2010; Meeuwissen et al, 2011; Palva et al, 2011). In these studies, the increasing of alpha band activity has been interpreted as a necessary mechanism to improve memory abilities.

More related to our work, the reduction in alpha power has also been observed during memory tasks and its meaning has been subjected to several interpretations. In one hand, it could reflect a lack of inhibition over task-irrelevant regions, which subsequently would affect performance (Jensen and Mazaheri, 2010). On the other hand, could be that these reduced values reflect a pathological pattern specific of MCI. In this line, Van Strien et al. (2005) observed alpha power increases during the detection of previously presented items suggesting its role in recognition processes. In addition, the reduction of posterior alpha power has been defined as the hallmark of mild AD (Babiloni et al., 2004) and as the discriminator of MCI subjects who convert to AD (Huang et al., 2000) during rest conditions. In line with these interpretations, Van der Hiele et al., (2007b) observed a decrease in alpha activity in AD patients which correlated with a worse performance on cognitive tests. Taking all these results together, we suggest that the decrease in alpha power observed in the MCI participants could be indicating a failure of the system to use a brain mechanism necessary to improve memory function.

Similarly to alpha band results, MCI subjects also showed less gamma power values, compared to controls, over left parietal regions between 372-489 ms. Gamma band oscillations have been proposed to play a key role in the synchronization of the cortical networks involved in object representation, attention and memory processes (Tallon-Baudry et al., 1999; Kaiser and Lutzenberger, 2003; Daskalakis et al., 2008; Schneider et al., 2008), and modifications have been related with brain degenerative pathologies such as MCI (Stam et al., 2002; Koenig et al., 2005). Thus, this decreased in

power seems to reflect a difficulty to execute the fast frequency mechanisms necessary to communicate information in the brain.

Taking together the reduction in power on high frequency bands, previous neuroimaging literature has considered brain hypoactivation as dysfunctional due to its relation to reduced task performance in AD patients (Small et al., 1999; Celone et al., 2006; Han et al., 2009; Clément and Belleville, 2010). According to this interpretation, any deviant activity from the pattern shown by the control group would be considered pathological.

Therefore, based on the literature and on the fact that we did not find any correlation between cognitive performance and power in beta, alpha and gamma bands, we suggest that these patterns of activity could represent neuronal dysfunction underlying the MCI pathology during the execution of this memory task. However, further studies would be suitable to better delineate the meaning of these patterns.

In sum, our results point towards a modulation of the neuronal oscillatory activity which reflects the existence of compensatory and dysfunctional mechanisms in the MCI brain. The significance of the compensation/ dysfunction duality is still an open issue. Further, longitudinal studies which evaluate whether brain anatomical alterations in MCI or brain activity changes, as the observed in the present study, manifest stable predictor patterns to AD are very relevant since they can offer highly useful information for diagnosis, prognosis and interventions (Bajo et al., 2012; Geroldi et al., 2006). Due to the probable transient nature of these mechanisms and their relationship to several factors, such as disease onset and its accumulating underlying neuropathology, brain/cognitive resources, genetics and/or environmental influences, the inclusion of these factors in future studies would improve our knowledge of MCI and its progression to AD (Feldman et al., 2010).

Conclusions

To conclude, our results suggest that even in the presence of objective memory alterations, the MCI's brain is able to match control subject's memory performance by modulating theta band power in frontal regions early after target stimulus onset. It would be interesting to assess if these processes could be enhanced by cognitive training.

The present report characterized the duality of oscillatory brain responses in MCI subjects and aimed to overcome some of the traditional difficulties in the analysis of neuronal electromagnetic data: 1) the assumption of the stationary nature of neurophysiological signals, and 2) the localization of oscillatory generator sources. Additionally, future studies should evaluate: 1) brain oscillatory patterns along the continuum to AD, 2) brain patterns between progressive and stable MCI subjects, 3) the influence of factors, such as advanced neuropathology, brain/cognitive reserve, genetic and/or environmental influences and 4) connectivity between brain regions.

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Disclosure statement

There are no actual or potential conflicts of interest.

Figure Legends

Figure1. Schematic illustration of experimental and analysis protocol: 25 elderly subjects underwent MEG recordings while performing a continuous recognition memory task. From signals in sensor space, oscillatory generators are localized using minimum-norm estimation procedure (MNE) in both, time and frequency, domains by means of wavelet transform. Only statistical differences between groups are shown.

Figure2. This figure shows statistical differences of target stimuli in spatial-time-frequency patterns between MCI and healthy controls in theta, alpha, beta and gamma spectral bands. Frequency band, group differences and corresponding p values are shown in left. A time axis is included to remark when differences occur.

Figure3. This figure shows the significant correlations ($r = 0.692$, $p<0.03$) between the theta power changes and LM-I subtest performance. The Y axis shows the percentage of MCI's power compared to controls. The percentage was calculated based on the statistically significant sources and time windows of the theta band. The X axis shows the number of items recalled in LM-I by MCI subjects.