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Title: "Differential patterns of functional connectivity in Progressive and Stable Mild Cognitive Impairment subjects"

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Differential patterns of functional connectivity in Progressive and Stable Mild Cognitive Impairment subjects

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Abstract

It is now widely accepted that AD is characterized by a functional disconnection between brain regions. The disease appears to begin up to decades prior to clinical diagnosis. Therefore, in the present study we combined Magnetoencephalography, a memory task and functional connectivity analysis in Mild Cognitive Impairment (19) subjects in order to identify functional connectivity patterns that could characterize subjects who would eventually go on to develop the disease. We monitored 19 subjects and finally 5 of them developed Alzheimer Disease. These progressive patients showed a differential profile of functional connectivity values compared to those patients that remained stable over time. Specifically there were higher synchronisation values over parieto-occipital regions and over the anterior frontal region in α and β frequency bands. The fact that we only include hit responses to analyze functional couplings reinforces the idea that Progressive Mild Cognitive Impairment subjects over-synchronize brain networks, in these two frequency bands (previously associated with working memory mechanisms), to compensate and achieve a level of performance in the memory task that is similar to the rest of the participants. The involvement of these brain regions in Aβ accumulation and its possible associations with hyper-synchronization are

also discussed.

Introduction

There is growing evidence that brain networks are functioning in a balance between segregation and integration of information processing, where regions with different levels of functional specialization coexist (Tononi et al, 1994). These cortical networks appear to be significantly disrupted (Stam et al, 2009) by the neuronal death and synapse loss characterizing Alzheimer's disease (AD), leading to the idea that AD may be a disconnection syndrome (Morrison et al, 1986). Since these pathological signs appear to begin up to decades prior to the diagnosis of AD (Braak & Braak, 1991) the use of methodologies that could study the flow of information transmission between brain regions could improve the early diagnosis of the disease and, even more importantly, could be used to predict who will develop dementia. One of these methodologies could be functional connectivity. Functional connectivity indicates the statistical interdependencies between two physiological signals which provide information about functional interactions between the corresponding brain regions (Friston et al, 1994).

Thus, it is of interest to evaluate whether functional connectivity profiles are affected in clinical conditions such as Mild Cognitive Impairment (MCI), considering its high rate of conversion to dementia (10 to 15% per year develop dementia; Petersen et al, 1999). Thus, MCI provides a unique opportunity to investigate physiological markers, such as functional connectivity, to predict who will develop dementia.

In the present study, we record oscillatory brain magnetic activity during a memory task using MEG, with the aim being to evaluate whether PMCI (progressive MCI) patients show a differential profile of functional connectivity values compared to those patients that remain stable over time (Stable MCI; SMCI) and compared to healthy aging (HA) subjects. Previous results revealed higher

brain activity in MCI subjects (Dickerson et al, 2005; Maestu et al, 2008). In addition, higher synchronisation was observed both in the thalamo-cortical circuit (Cantero et al, 2009) and between cortical regions (Bajo et al, in press), reflecting a compensatory mechanism. Based on these previous results, we predict that PMCI subjects will demonstrate an overuse of this compensatory mechanism in the sense of higher synchronisation values than SMCI and HA. To the best of our knowledge this is the first study to evaluate how MEG functional connectivity values could predict who will develop dementia.

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: 19 participants had been diagnosed as amnestic-MCI subjects and 19 as healthy aging (HA) participants. After two and a half years of follow-up five MCI patients converted to AD (PMCI).

MCI diagnosis was established according to the criteria proposed by Petersen et al. (Petersen, 2004). Their clinical evolution is monitored every six months with a clinical interview and a neuropsychological assessment. More information could be found elsewhere (Bajo et al, in press). The study was approved by the local ethics committee.

Stimuli and task

A modified version of the Sternberg´s letter-probe task (deToledo-Morrell et al., 1991; Maestu et al., 2001) was used. A set of five letters was presented and the participants were asked to keep the

letters in mind and then raise a finger every time they detect a letter that was in the previous list.

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. Only hits were considered for further analysis because we were interested in evaluating the functional connectivity patterns which support recognition success.

In-house Fortran code was used to implement the (Synchronization Likelihood) SL algorithm as described by Stam and van Dijk (2002). The following frequency bands were considered: alpha1 (α1, 8-11 Hz), alpha2 (α2, 11-14 Hz), beta1 (β1, 14-25 Hz), beta2 (β2, 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 (Montez et al., 2006).

Statistical analysis

Nonparametric permutation testing (Ernst, 2004) was applied to find channel pairs with significant differences between groups.

Results

PMCI, SMCI and HA did not show differences in task performance ($p>0.05$). All MEG outcomes were significant in α1, α2 and β1 frequency bands.

PMCI subjects, in comparison to the SMCI showed higher synchronization values over two independent clusters: the parieto-temporal region and the prefrontal region essentially in the α1 and

α2. In the β1 band this effects were still present although the frontal synchronization effect was diminished with and increased values over temporal sensors bilaterally. When PMCI were compared to HA, PMCI showed a higher interhemispheric frontal and parieto-occipital synchronization essentially in the α bands, while in the β1 band the posterior synchronization diminishes. SMCI subjects showed higher synchronization than HA over the central region and between frontal regions in the α and β1 frequency bands (see Figures 1 and 2). The comparison between controls and MCI subjects as a group was described in detail in Bajo et al. (in press) and will not be described here.

FIGURE 1

FIGURE 2

Discussion

In the present study, by studying MCI subjects that do and do not go on to develop dementia, we were able to describe a differential profile of functional connectivity between them, and also in comparison with HA subjects. PMCI subjects showed higher synchronisation values than SMCI subjects over parieto-occipital regions and over the anterior frontal region. This high synchronisation, also appears when comparing with the control group. Functional connectivity studies with EEG indicate higher connectivity values in MCI subjects in comparison with healthy aging subjects in the upper α thalamo-cortical circuit (Cantero et al, 2009) as well as a relationship between functional connectivity between temporo-parietal regions in the α band and anatomical connectivity in predominantly posterior white matter tracts (Teipel et al, 2009). Similarly, fMRI

studies using functional connectivity in MCI patients have also shown increases in functional connectivity values in MCI patients as compared with healthy age-matched participants (Bai et al., 2008). Since the evolution of AD is characterized by the progressive loss of functional connectivity within neocortical association areas (Stam et al, 2009), the hyper-connectivity or the increased activity found in MCI subjects could be a compensatory mechanism for the inefficiency of the memory networks (Dickerson et al, 2005). Thus, our PMCI subjects appear to be overusing such compensatory mechanisms 2.5 years prior to developing AD. Therefore, it can be concluded that the higher the functional connectivity values the higher the risk for the development of AD. It is of interest that PMCI subjects showed higher connectivity in the α and β range as these frequency bands have been previously associated with working memory mechanisms (Palva et al., 2010). The fact that we only include hit responses to analyze functional couplings reinforces the idea that PMCI subjects over-synchronize brain networks in these two working memory frequency bands, to compensate and achieve a level of performance in the memory task that is similar to the rest of the participants.

In addition, these two brain regions (where PMCI present high synchronization) have been previously associated with increased accumulation of the Amyloid-β peptide in both AD (Apostolova & Thompson, 2008) and MCI patients (Nordberg, 2008). This leads to the question of what the relationship between brain hyper-synchronization and the accumulation of this peptide in MCI or AD patients could be. Cirrito et al. (2005), in an elegant study, showed that the increase of synaptic activity lead to a rapid increase of Amyloid-β peptide levels in specific brain regions. Thus, this study indicates that synaptic activity may modulate the neurodegenerative disease process. Bearing in mind that MEG signals are the consequence of postsynaptic electrical currents within the dendron, the increased activity observed in PMCI subjects over frontal and parieto-occipital areas could be a risk factor for Amyloid-β deposition and, as a consequence, a risk factor for a subsequent

cognitive decline. Thus, this apparently “compensatory” mechanism developed by amnestic-MCI subjects could in fact turn out to be a risk factor for the development of AD.

Future studies should evaluate whether these profiles of synchronization 1) could be associated with genetic profiles such as APOE4 or 2) reflect an accumulation of Amyloid-β peptide in similar regions.

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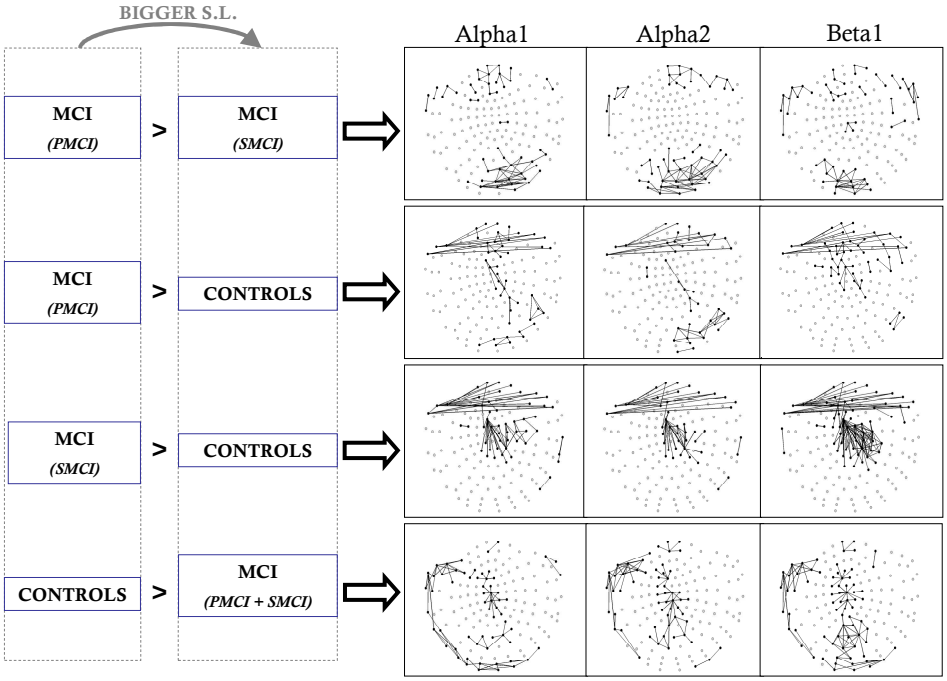
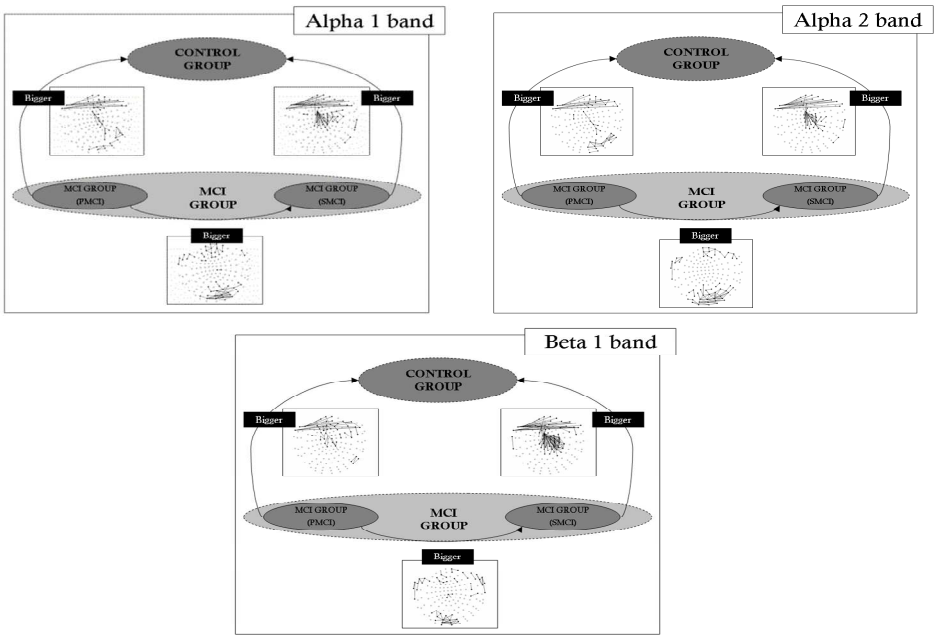
FIGURE LEGENDS:

Figure 1: *Significant differences in Synchronization Likelihood between electrode pairs for different frequency bands and groups (PMCI, SMCI and Controls).*

Figure 2: *Significant differences in Synchronization Likelihood between electrode pairs for different frequency bands and groups (PMCI, SMCI and Controls).*


BIGGER S.L.
Alpha1
Alpha2
Beta1
MCI (PMCI) > MCI (SMCI)
MCI (PMCI) > CONTROLS
MCI (SMCI) > CONTROLS
CONTROLS > MCI (PMCI + SMCI)


Alpha 1 band
Alpha 2 band
Beta 1 band
CONTROL GROUP
Bigger
MCI GROUP (PMCI)
MCI GROUP
MCI GROUP (SMCI)