NeuroImage: Clinical 6 (2014) 214–221

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

The Default Mode Network is functionally and structurally disrupted in amnestic mild cognitive impairment — A bimodal MEG–DTI study

Pilar Garcés[a,b,*], José Ángel Pineda-Pardo[a], Leonides Canuet[a], Sara Aurtenetxe[a,c], Maria Eugenia López[a,c], Alberto Marcos[d], Miguel Yus[e], Marcos Llanero-Luque[f], Francisco del-Pozo[a], Miguel Sancho[b], Fernando Maestú[a,c]

[a] Laboratory of Cognitive and Computational Neuroscience (UCM–UPM), Centre for Biomedical Technology, Pozuelo de Alarcón, Madrid 28223, Spain
[b] Department of Applied Physics III, Faculty of Physics, Complutense University of Madrid, Madrid 28040, Spain
[c] Department of Basic Psychology II, Faculty of Psychology, Complutense University of Madrid, Madrid 28223, Spain
[d] Neurology Department, Hospital Clínico San Carlos, Madrid 28040, Spain
[e] Radiology Department, Hospital Clínico San Carlos, Madrid 28040, Spain
[f] Centre for Prevention of Cognitive Impairment, Madrid 28006, Spain

ARTICLE INFO

Article history:
Received 6 August 2014
Received in revised form 27 August 2014
Accepted 5 September 2014
Available online 10 September 2014

Keywords:
Default mode network
Mild cognitive impairment
Magnetoencephalography
Functional connectivity
Alpha band
Structural connectivity
Diffusion tensor imaging
Tractography

ABSTRACT

Over the past years, several studies on Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) have reported Default Mode Network (DMN) deficits. This network is attracting increasing interest in the AD community, as it seems to play an important role in cognitive functioning and in beta amyloid deposition. Attention has been particularly drawn to how different DMN regions are connected using functional or structural connectivity. To this end, most studies have used functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET) or Diffusion Tensor Imaging (DTI). In this study we evaluated (1) functional connectivity from resting state magnetoencephalography (MEG) and (2) structural connectivity from DTI in 26 MCI patients and 31 age-matched controls. Compared to controls, the DMN in the MCI group was functionally disrupted in the alpha band, while no differences were found for delta, theta, beta and gamma frequency bands. In addition, structural disconnection could be assessed through a decreased fractional anisotropy along tracts connecting different DMN regions. This suggests that the DMN functional and anatomical disconnection could represent a core feature of MCI.

1. Introduction

Mild Cognitive Impairment (MCI) is a clinical condition that is often seen as an intermediate stage between normal aging and Alzheimer's disease (AD). MCI patients show a cognitive decline that is not severe enough to be classified as dementia. However, they have a higher conversion rate to dementia than their age-matched controls, particularly of the Alzheimer type (10–15% annually for MCIs versus 1–4% for controls) (Petersen and Negash, 2008; Petersen, 2001). Over the past few years a lot of attention has been given to this MCI stage, as a deeper understanding of its pathological basis could help understand or delay AD.

The pathophysiology of AD involves the Default Mode Network (DMN). This network was first introduced in Raichle et al. (2001). and has garnered increasing attention from the neuroscience and neurology communities ever since (for a review, see Rosazza and Minati, 2011). It is highly active during an idle state, it deactivates during task performance, and it includes brain regions such as the precuneus, posterior and anterior cingulate, and the inferior parietal cortex (Buckner et al., 2008; Greicius et al., 2003; Raichle and Snyder, 2007). The precuneus and posterior cingulate cortex have been found to be relevant in AD as they show decreased metabolic activity (Matsuda, 2001) and accumulate beta-amyloid plaques at an early stage in the disease (Mintun et al., 2006). DMN alterations such as decreased activity and connectivity have been reported in AD and MCI (Agosta et al., 2012; Greicius et al., 2004; Jones et al., 2011; Qi et al., 2010; Rombouts et al., 2005; Sorg et al., 2007). Furthermore, these alterations were found to be related to the severity of the disease and its progression (Brier et al., 2012; Petrella et al., 2011).

To date, functional Magnetic Resonance Imaging (fMRI) is the most widespread technique used to explore the DMN in MCI or AD. Blood-oxygenation-level-dependent (BOLD) fMRI signals measure hemodynamic responses to neuronal activity with great spatial resolution and

* Corresponding author at: Laboratory of Cognitive and Computational Neuroscience (UCM-UPM), Centre for Biomedical Technology (CTB), Campus de Montegancedo s/n, Pozuelo de Alarcón, Madrid 28223, Spain.
E-mail addresses: pilar.garces@ctb.upm.es (P. Garcés), joseangel.pineda@ctb.upm.es (J. Ángel Pineda-Pardo), leonides.canuet@ctb.upm.es (L. Canuet), sara.aurtenetxe@ctb.upm.es (S. Aurtenetxe), meugenia.lopez@ctb.upm.es (M.E. López), amarcosdolado@gmail.com (A. Marcos), miguel_yus@yahoo.com (M. Yus), mllanero@gmail.com (M. Llanero-Luque), francisco.delpozo@ctb.upm.es (F. del-Pozo), msancho@ucm.es (M. Sancho), fernando.maestu@ctb.upm.es (F. Maestú).

http://dx.doi.org/10.1016/j.nicl.2014.09.004

have led to the discovery of multiple resting state networks, including the DMN. Other imaging modalities can also provide insight into DMN integrity in MCI: structural MRI reveals brain atrophy; Diffusion Tensor Imaging (DTI) reconstructs white matter tracts; Positron Emission Tomography (PET) detects metabolic activity or beta-amyloid plaques and magnetoencephalography/electroencephalography (MEG/EEG) measures magnetic/electric fields generated by neural currents. Based on this fact, researchers have combined fMRI (often controlling for brain atrophy with T1-weighted structural MRI) with other neuroimaging modalities such as PET (Hedden et al., 2009; Sheline et al., 2010; Sperling et al., 2009) and DTI (Wee et al., 2012), or DTI with PET (Bozoki et al., 2012) to investigate DMN functional and structural connectivity impairment in AD and MCI.

While fMRI and PET give an indirect estimation of neural activity, EEG and MEG are direct measures of neural firing. Therefore, these neurophysiological techniques enable us to gain a better understanding of the time–frequency dynamics of the DMN, providing us with useful information as to how its regions are connected at different frequency bands. Complementary structural information about DMN connectivity is given by DTI, as it enables the modeling of the white matter connections that support the network. Using this technique, we can compute direct or weighted structural connectivity measures that estimate the number of tracts connecting two regions and the integrity of anatomical connections, respectively. However, thus far, the combination of MEG and DTI has not been used to unravel DMN abnormalities in MCI. In this study, we investigated the DMN in MCI patients compared to age-matched controls using resting-state MEG and DTI data to extract both functional and structural networks. The purpose of the study was to determine the functional connections that were altered in MCI relative to controls at different frequency bands, and how this relates to the underlying structural network. For that, source space MEG functional connectivity (FC) was computed and two different structural connectivity (SC) measures were used to evaluate whether the amount of tracts or their integrity influences the organization of the functional networks. Our initial hypothesis is that both functional and structural connections will be significantly impaired in MCI patients and there will be a strong correlation between functional and structural connectivity abnormalities.

2. Materials and methods

2.1. Subjects

This study included 26 patients with a diagnosis of amnestic-MCI and 31 age-matched controls. MCI patients were diagnosed by clinical experts. Criteria for MCI included: (1) memory complaint confirmed by an informant, (2) normal cognitive function, (3) none or minimal impairment in activities of daily life, (4) abnormal memory function, and (5) not being sufficiently impaired to meet the criteria for dementia (Grundman et al., 2004). Table 1 summarizes the subject's characteristics.

Additionally, all participants were in good health and had no history of psychiatric or other neurological disorders (other than MCI). They underwent an MRI brain scan to rule out infection, infarction or focal lesions. Meeting any of the following conditions was considered an exclusion criterion: Hachinski score (Rosen et al., 1980) higher than 4, Geriatric Depression Scale score (Yesavage et al., 1982–1983) higher than 14, chronic use of anxiolytics, neuroleptics, narcotics, anticonvulsants, or sedative–hypnotics or a history of alcoholism. MCI patients underwent medical tests to rule out possible causes of cognitive decline such as B12 vitamin deficiency, thyroid problems, syphilis, or HIV. The investigation was approved by the local Ethics Committee.

Table 1
Subject characteristics. Data are given as mean ± standard deviation. M = males, F = females, educational level was grouped into five levels: 1: illiterate, 2: primary studies, 3: elemental studies, 4: high school studies, 5: university studies. MMSE = Mini mental state examination score. Controls and MCIs differed in MMSE ($p = 0.0012$) and educational level ($p = 0.03$), and did not differ in age ($p = 0.39$) or sex ($p = 0.44$).

	n	Age (years)	Sex (F/M)	MMSE	Educational level
Control	31	70.8 ± 4.2	21/10	29.5 ± 0.7	3.5 ± 1.2
MCI	26	72.5 ± 6.7	15/11	27.7 ± 2.4	2.8 ± 1.3

2.2. MEG acquisition

Three-minute MEG resting-state recordings were acquired at the Center for Biomedical Technology (Madrid, Spain) using an Elekta Vectorview system with 306 sensors (102 magnetometers and 204 planar gradiometers), inside a magnetically shielded room (Vacuumschmelze GmbH, Hanau, Germany). During the measurements, subjects sat with their eyes closed and were instructed to remain calm and move as little as possible. A Fastrak Polhemus system digitized each subject's head and four coils were attached to the forehead and mastoids, so that the head position with respect to the MEG helmet was continuously determined. Activity in electrooculogram channels was also recorded to keep track of ocular artifacts.

Signals were sampled at 1000 Hz with an online filter of bandwidth 0.1–300 Hz. Maxfilter software (version 2.2, Elekta Neuromag) was used to remove external noise with the temporal extension of the signal space separation (tsss) method with movement compensation (Taulu and Simola, 2006).

2.3. MRI acquisition

3D T1 weighted anatomical brain MRI scans were collected with a General Electric 1.5 T magnetic resonance scanner, using a high-resolution antenna and a homogenization PURE filter (Fast Spoiled Gradient Echo (FSPGR) sequence with parameters: TR/TE/TI = 11.2/4.2/450 ms; flip angle 12°; 1 mm slice thickness, a 256 × 256 matrix and FOV 25 cm). For MEG source analysis, the reference system of the T1 volumes was transformed manually using 3 fiducial points and head shape, until a good match between MEG and T1 coordinates was reached. Diffusion weighted images (DWI) were acquired with a single shot echo planar imaging sequence with the following parameters: TE/TR 96.1/12,000 ms; NEX 3 for increasing the SNR; 2.4 mm slice thickness, 128 × 128 matrix and 30.7 cm FOV yielding an isotropic voxel of 2.4 mm; 1 image with no diffusion sensitization (i.e., T2-weighted b_0 images) and 25 DWI ($b = 900$ s/mm^2).

2.4. Definition of the Regions of Interest

For this bimodal connectivity analysis, we defined Regions of Interest (ROIs) in the individual's structural T1 volume using the Freesurfer (version 5.1.0) cortical parcellation in 66 regions (Desikan et al., 2006), such as in Hagmann et al. (2008) and Honey et al. (2009). We selected four ROIs per hemisphere, which are the most common brain structures included in the DMN (Buckner et al., 2008; Greicius et al., 2003; Raichle and Snyder, 2007): precuneus (lPr and rPr), anterior cingulate (lAC and rAC), posterior cingulate (lPC and rPC) and inferior parietal (lIP and rIP).

2.5. MEG functional connectivity (FC)

MEG preprocessing and source reconstruction were performed with FieldTrip software (Oostenveld et al., 2011).

2.5.1. MEG source reconstruction

First, ocular, jump and muscular artifacts were identified and located in the 3 minute resting state recordings. Then, the continuous resting time-series were segmented into artifact-free segments of 4 s. All subjects had a minimum of 16 artifact-free segments (control: (27.5 ± 5.9), MCI: (27.2 ± 6.1)). Data was filtered in the 1–45 Hz band for spectral analysis and in delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), low