DIFFERENCES IN DMN FUNCTIONAL CONNECTIVITY BEFORE AND AFTER CLINICAL DIAGNOSIS OF AMNESTIC MCI

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Target audience: Scientists and clinicians interested in early diagnosis of cognitive impairments using resting state analysis.

Purpose: To analyze functional connectivity differences in the Default Mode Network (DMN) of patients before and after being diagnosed with Amnestic Mild cognitive impairment (aMCI) and their differences with healthy controls (HC).

Introduction: Resting state fMRI analysis allows for the evaluation of connectivity in resting state networks[1]. Significant connectivity differences in one of these networks, the DMN, have been reported between controls and patients with MCI or Alzheimer's Disease[2,3] patients. This work shows the DMN functional connectivity differences in aMCI patients before and after being diagnosed and their differences with healthy subjects. This will lead to a deeper understanding of the evolution of this disease and to evaluate the possibility of using DMN functional connectivity as an early biomarker.

Methods: *Subjects:* 685 healthy volunteers (aged between 70-85 years) from the Vallecas Project, a follow-up study to assess normal healthy ageing and the appearance of neurodegenerative diseases, underwent cognitive tests in order to assess normality. Two sessions per subject, separated in time 399±22 days, were included in the analysis. After the second examination, 11 subjects started to show cognitive deterioration and were diagnosed as aMCI. A two-group study comparing the 11 converters from an age and gender matched group of HC subjects was performed. First and second session of the converter group was named as "aMCI-1" and "aMCI-2" respectively.

Stimuli and experiment: Subjects underwent closed eyes resting-state fMRI for 5 minutes.

Data acquisition: MRI data were collected using a GE Signa 3.0 T MR Scanner. Resting-state functional images were acquired in a single run of 120 volumes, using a GE-EPI pulse sequence whose parameters were: TR=2.5s, TE=27.5ms, voxel dimensions=2.5x2.5x2.6mm, number of slices=32. Also, sagittal 3D T1 weighted images were acquired with: TR=10.024ms, TE=4.56ms, TI=600ms, NEX=1, acquisition matrix=288x288, full brain coverage, resolution=1x1x1mm, flip angle=12º parameters.

Data preprocessing: Functional imaging preprocessing was carried out using FEAT from FMRIB's Software Library (FSL) and AFNI. The preprocessing steps were: despiking, slice timing correction, motion correction, fieldmap correction, spatial smoothing (FWHM=6mm) and temporal high pass filtering (100s). After fieldmap correction, average white matter and cerebrospinal fluid time series and motion correction parameters were regressed out in order to reduce non-neural signal fluctuations. Finally, all images were normalized to a standard Montreal Neurological Institute template. Grey matter volume estimations were performed with FreeSurfer in order to introduce them as a covariate in the statistical analysis[4].

Data analysis: FSL dual regression was applied to obtain the individual spatial maps related to the DMN spatial map reported by Smith et al.[2]. Permutation statistics were computed with FSL-randomise to evaluate differences: aMCI-1 vs aMCI-2, aMCI-1 vs HC, aMCI-2 vs HC. Age, gender and grey matter volume were included as confounding factors. The statistical analyses were considered significant for a $p<0.005$, threshold free cluster enhancement (tfce) corrected.

Results: Significant aMCI longitudinal connectivity decrease was found on left parahippocampal gyrus and left thalamus (Fig. 1A). Lesser functional connectivity in both aMCI-1 and aMCI-2 compared to HC was observed in thalamus, Broadmann 30 and anterior cingulate (blue/green areas in Fig. 1B&C). However, hyper-functional connectivity was also detected, especially in precuneus, angular gyrus, left postcentral gyrus and left middle temporal gyrus (red/yellow Fig. 1B&C). Larger regions appeared in aMCI-1 than in aMCI-2 compared to HC (the number of statistically significant different voxels increases in 348%).

Discussion: DMN functional connectivity impairment and compensation effects coexist in aMCI compared to HC[5]. These results corroborate hyper-functional connectivity in precuneus[6] and left middle temporal gyrus[5]. They also show that this compensation effect is significant at least one year before aMCI diagnosis and covers larger areas. Initial functional connectivity impairment seems to be focused on left thalamus[7] and hippocampus, which could precede the reported hippocampi atrophy in aMCI[3].

Conclusion: DMN functional connectivity alterations are related to the evolution of aMCI and they happen before clinical diagnosis. Therefore, they could be useful as an early biomarker for aMCI or even for AD, because aMCI patients are at risk of developing this disease[2,3]. These findings will be proved in the coming years in this follow-up study, where more progress to MCI and AD diagnosis is expected.

References: [1] Smith, Stephen M., et al. Correspondence of the brain's functional architecture during activation and rest. Proceedings of the National Academy of Sciences106.31 (2009): 13040-13045. [2] Beason-Held, L. L., M. A. Kraut, and S. M. Resnick. Stability of default-mode network activity in the aging brain. Brain imaging and behavior 3.2 (2009): 123-131. [3] Sheline, Yvette I., and Marcus E. Raichle. Resting State Functional Connectivity in Preclinical Alzheimer's Disease. Biological psychiatry (2013). [4] He Y. et al. Regional coherence changes in the early stages of Alzheimer's disease: a combined structural and resting-state functional MRI study. NeuroImage, (2007): 488–500. [5] Qi, Zhigang, et al. Impairment and compensation coexist in amnestic MCI default mode network. Neuroimage 50.1 (2010): 48-55. [6] Bai, Feng, et al. Specifically progressive deficits of brain functional marker in amnestic type mild cognitive impairment. PLoS One 6.9 (2011): e24271. [7] Wang, Zhiqun, et al. Changes in thalamus connectivity in mild cognitive impairment: Evidence from resting state fMRI. European journal of radiology81.2 (2012): 277-285.

Acknowledgements: This work has been partially granted by the project TEC2012-39095-C03-01 of the Spanish Ministry of Economy and Competiveness.

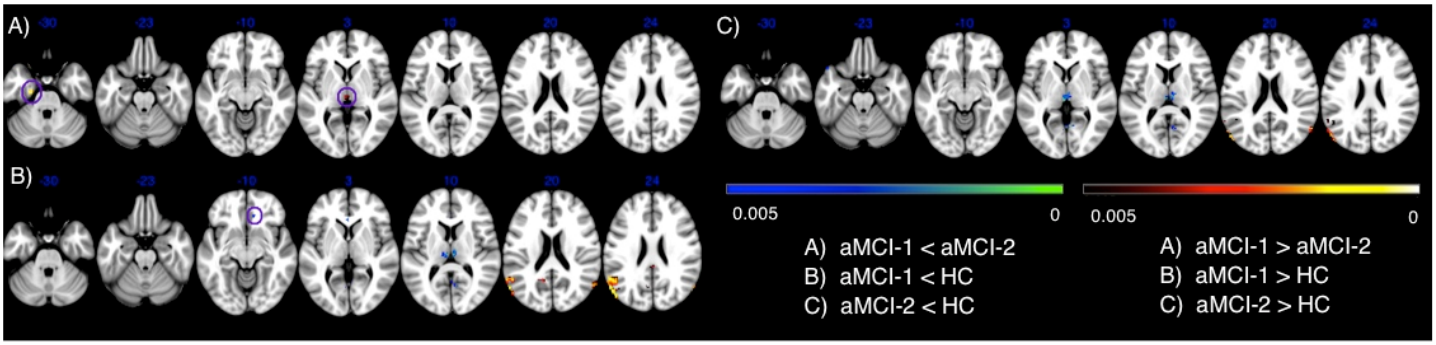

Figure 1: Significant differences in DMN functional connectivity ($p < 0.005$, tfce corrected): A) aMCI-1 vs aMCI-2, B) aMCI-1 vs HC-1, C) aMCI-2 vs HC-1.