The impact of white matter hyperintensities on brain functional connectivity in amnestic mild cognitive impairment patients.

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TARGET AUDIENCE: Neuroscientists with an interest in the dementia.

PURPOSE Amnestic Mild Cognitive Impairment (a-MCI) is a heterogeneous condition characterized by memory deficits in isolation or associated with other cognitive dysfunctions and is recognized as a transitional state between normal aging and dementia. These impairments are associated with abnormal structural and functional connections among brain regions. White matter hyperintensities (WMHs) are commonly observed in MCI patients and they are associated with higher risk of developing dementia. However, their impact on structural and functional connections and on cognition is still not fully understood. The aim of the study is to investigate functional connectivity (FC) alterations within the default mode network (DMN) in a-MCI patients with different WMH burden, using resting-state functional magnetic resonance imaging (RS-fMRI).

MATERIAL AND METHODS We recruited 44 a-MCI patients and 18 healthy subjects (HS). All participants underwent clinical and neuropsychological evaluations, structural and RS-fMRI scanning at 3T (Magnetom Allegra, Siemens, Erlangen, Germany). The MRI acquisition protocol included: (1) Dual-echo TSE (repetition time [TR]=6.190msec, echo time [TE]=12/109 msec); (2) FLAIR (TR=8.170msec, TE=96 msec, inversion time [TI]=2.100 msec); (3) 3D MDEFT (TR=1338 ms, TE=2.4 ms, Matrix=256x224x176, in–plane FOV=250x250 mm2, slice thickness=1 mm); (4) T2* weighted EPI sensitized to BOLD contrast (TR=2080 ms, TE=30 ms, 32 axial slices parallel to AC-PC line, matrix=64x64, pixel size=3x3 mm2, slice thickness=2.5 mm, flip angle:70°). BOLD EPIs were collected during rest for 7 min and 20 s, resulting in a total of 220 volumes. During this acquisition, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. **MRI data analysis:** WMHs were first identified by consensus by two trained observers on TSE images using a semi-automated local thresholding contouring software (Jim 4.0. Xinapse System. Leicester. UK. http://www.xinapse.com/). The median WMH volume across the group was used as threshold to classify patients in two different groups (High volume –H and Low volume –L). In order to better characterize the distribution of WMHs in our groups, we create a WMHs composite frequency distribution map by normalizing the lesions mask of every subject to Montreal Neurological Institute (MNI) space using FNIRT[2] (Fig. 1).

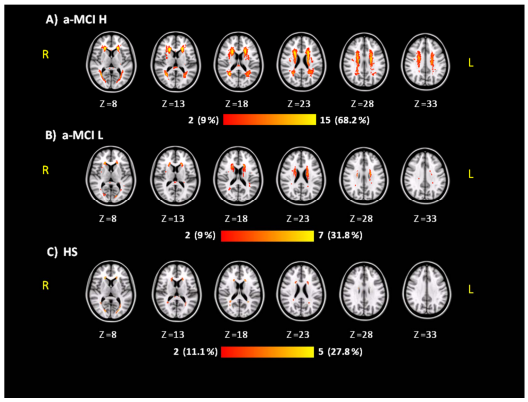

Fig 1 Voxel intensity values indicate the frequency of WMHs for each voxel

RS-fMRI data were processed using MATLAB R2007B (Math-Work, Natick, MA) and SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). The first 4 volumes of the functional images were discarded for signal equilibrium and adaptation of participant to scanning noise. Next, slice timing and head motion correction were performed, and the mean functional image was obtained for each participant. No participant exhibited head motion of >2 mm maximum translation or 2° rotation throughout the course of scan. The images were then normalized using the EPI template provided with SPM8. In-house software was used to remove, using a 3rd order polynomial fit, the global temporal drift, the realignment parameters, and the signal averaged over whole brain voxels. EPI images were then filtered using a phase-insensitive band-pass filter (pass band 0.01- 0.08 Hz) to reduce effects of low frequency drift and high frequency physiological noise. Finally, they were smoothed with an 8 mm^3 FWHM 3D Gaussian Kernel. Each MDEFT-image was segmented using the standard SPM8 algorithm and the resulting grey matter images used to compute each participants total grey matter volume.Group ICA Toolbox (http://mialab.mrn.org /software/) was then used in order to identify 20 independent components. The DMN component was identified by visual inspection of the main effect maps with reference to established topographical maps, upon agreement of 3 observers.
Second level analysis was performed in SPM8 using a full factorial design to compare FC of the DMN between the three different groups (HS, a-MCI H, a-MCI L) adding age, gender and GM volume as covariates. Results were considered significant for p<0.05 FWE corrected at cluster level.

RESULTS The neuropsychological assessment revealed that both a-MCI groups performed significantly worse than controls on memory tasks ($F_{2,59} = 18.64$ [$P = .000001$].There were no significant differences between the 2 a-MCI groups, but a-MCI H group performed significantly worse than controls in the Modified Card Sorting Test ($F_{2,50} = 8.42$ [$P = .0007$]).
The second level analysis revealed a significant (pFWE<0.05) decreased of DMN FC in a-MCI H with respect to both a-MCI L and HS groups in the thalamus (Fig.2). In particular, the areas of reduced FC are within a thalamic portion mainly connected to prefrontal and temporal cortex, according to the Oxford Thalamic Connectivity Probabilty Atlas available in FSL[3](Fig 2).

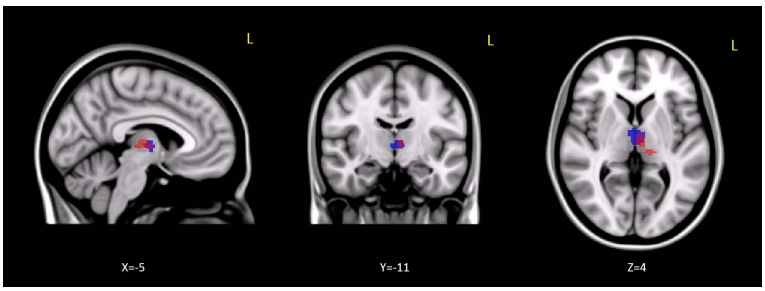

Fig 2 Pattern of reduced FC in the a-MCI H with respect to both a-MCI L (red) and HS (blue)

DISCUSSION The decreasing of functional correlations between thalamic regions and specific cortical areas that we found in a-MCI H patients, could reflect a reduced integrity of these networks that can be due to a greater WMHs burden. Our hypothesis is that the presence of WMHs in a-MCI patients could induce further alterations of FC thus playing an additive role in the development of cognitive decline normally observed in a-MCI patients.

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