WHITE MATTER LESIONS ACCOUNT FOR APATHY SYMPTOMS IN AMNESTIC MILD COGNITIVE IMPAIRMENT: A VOXEL BASED LESION SYMPTOM MAPPING STUDY

Mario Torso[1], Laura Serra[1], Giovanni Giulietti[1], Roberta Perri[2], Lucia Fadda[2,3], Barbara Spanò[1], Camillo Marra[4], Mara Cercignani[1,5], Carlo Caltagirone[2,3], and Marco Bozzali[1]

[1]Neuroimaging Laboratory, Santa Lucia Foundation, IRCCS, Rome, Italy, [2]Department of Clinical and Behavioural Neurology, Santa Lucia Foundation, IRCCS, Rome, Italy, [3]Department of Neuroscience, University of Rome "Tor Vergata", Rome, Italy, [4]Institute of Neurology, Università Cattolica, Rome, Italy, [5]Clinical Imaging Sciences Centre, Brighton & Sussex Medical School, Brighton, United Kingdom

TARGET AUDIENCE: Neuroscientists with an interest in dementia.

PURPOSE

Amnestic mild cognitive impairment (a-MCI), which is regarded as a frequent prodromal stage of Alzheimer disease (AD), is a heterogeneous condition characterized by memory deficits in isolation (single domain) or associated with impairments in other cognitive functions (multiple domain). Behavioral disorders and psychological symptoms (BPSD) are also commonly observed in a-MCI patients and have a substantial impact on the their quality of life. While white matter hyperintensities (WMHs) are often observed in patients with aMCI and AD, their contribution to the disease burden is still controversial. The aim of the present work was to assess, by using Voxel-based lesion–symptom mapping (VLSM)[1] analysis, the impact of WMHs on BPSD in patients with a-MCI.

MATERIAL AND METHODS

Thirty-one patients with a-MCI and 26 healthy controls (HS) underwent clinical and neuropsychological assessments and MRI scanning at 3T (Magnetom Allegra, Siemens, Erlangen, Germany). BPSD were assessed using the Neuropsychiatric Inventory-12 (NPI-12)[2]. The MRI acquisition included: 1) a dual-echo turbo spin echo [TSE] (TR=6190 ms; TE=12/109 ms); 2) a fast-FLAIR (Fluid attenuated inversion recovery) (TR=8170 ms. TE=96 ms. TI=2100ms); and 3) a 3D Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR=1338 ms. TE=2.4 ms; Matrix=256x224. n. slices=176; thickness=1 mm). **MRI data analysis:** We employed the Voxel-based Lesion Symptom Mapping (VLSM) approach, which allows to estimate the impact of lesions' localization on continuous measure, such as scores expressing behavioural symptoms. In the current study, the output of VLSM analysis is a statistical map expressing, for each lesion voxel, the probability of discriminating between two subgroups of patients reporting significantly different scores at a certain BPSD subscale. In each patient, WMHs were outlined using a semiautomatic thresholding technique (Jim 4.0 Xinapse System. Leicester. UK) Then, to perform the VLSM analysis, every lesion mask was normalized to the MNI space. T1 weighted volumes were segmented in GM, WM and CSF by SPM8-NewSegment. A binary brain mask was then obtained by combining the 3 segments and thresholding the resulting image. This mask was used to skull-strip the original TSE images. The skull-stripped TSE images were then affine transformed (12dof) to match the T1-weighted template brain in MNI coordinates available with FSL (MNI152_T1_1mm_brain). The same transformation was finally applied to the binary lesion mask to get the lesion mask normalized in MNI space. The normalized lesion masks and the NPI-12 scores that resulted more frequent and severe in our a-MCI group were entered as dependent variables in the VLSM analyses. The t-tests were confined to those voxels where at least 4 subjects had a lesion, to maintain a reasonable level of statistical power. The resulting statistical maps were corrected for multiple comparisons at cluster level using a permutation test with 1000 repetitions and accepting as significant p values of less than 0.05. Apathy, irritability, depression, anxiety and agitation NPI-12' sub-scores were individually considered as dependent variables in the VLSM analyses.

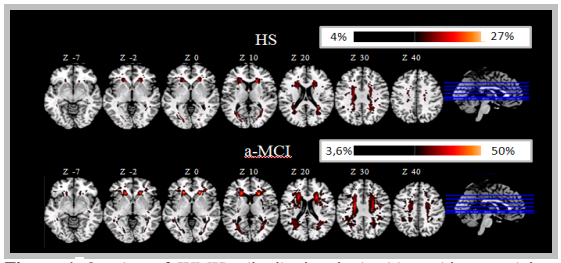

Figure 1 Overlap of WMHs distribution in healthy subjects and in patients with a-MCI.

RESULTS

As illustrated in Figure 1, a-MCI patients showed a more widespread distribution of WMHs than HS. In VLSM analysis run in a-MCI patients, apathy was the only BPSD whose score resulted to be significantly associated with a specific WMH localization (p=0.0070; p=0.0350). As shown in Figure 2, this localization involved the anterior thalamic radiation bilaterally (ATR). No significant associations were found between WMH distribution and other NPI-12 scores. Further, as pot-hoc analysis, Voxel Based Morphometry analysis (VBM) was used to investigate possible differences in regional GM volumes between a-MCI patients who reported presence of apathy at the NPI-12 and those who did not. No significant difference was found between the 2 subgroups.

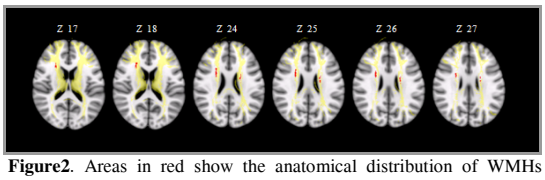

Figure2. Areas in red show the anatomical distribution of WMHs resulted to be significantly associated to the presence/severity of apathy symptoms in a-MCI patients. Lesions were located in the anterior thalamic radiation bilaterally (shown in yellow)

DISCUSSION

This study highlights a possible link between the anatomical distribution of WMHs and the presence of apathy in patients with a-MCI. This anatomical distribution was well confined to the ATR bilaterally, a WM bundle that connects the thalamus with the frontal lobe. As previously suggested by others[3], these findings reinforce the idea that disconnection is not only implicated in cognitive but also in behavioral symptoms of patients with AD since early clinical stages.

REFERENCES 1. Bates, E., Wilson, S.M., Saygin, A.P., Dick, F., Sereno, M.I., Knight, R.T., Dronkers, N.F.: Voxel-based lesion-symptom mapping, Nat. Neurosci. 6, 448–450, 2003. 2 Cummings JL: The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology 48, S10S16, 1997 3 Cummings JL: Frontal-subcortical circuits and human behavior. Arch Neurol; 50:873–880, 1993