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

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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 their quality of life. While white matter hyperintensities (WMHs) are often observed in patients with AD 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) 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 (HC) 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)1. The MRI acquisition included: 1) a dual-echo turbo spin echo [TSE] (TR=6190 ms; TE=1210/9 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). The 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 (Jinm 4.0 Xnapse System, Leicester, U.K ) 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 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). Apathy, irritability, depression, anxiety and agitation NPI-12' sub-scores were individually considered as dependent variables in the VLSM analyses. The t-tests were confined to 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.

RESULTS

As illustrated in Figure 1, a-MCI patients showed a more widespread distribution of WMHs than HC. 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 post-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.

DISCUSSION

This study highlights a possible link between the anatomical distribution of WMHs and the presence of apathy symptoms 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 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