Quantitative magnetization transfer imaging in normal aging, amnesic MCI and Alzheimer's disease

Giovanni Giulietti[1], Marco Bozzali[1], Laura Serra[1], Barbara Spano'[1], Barbara Basile[1], Roberta Perri[2], Camillo Marra[3], Carlo Caltagirone[2,4], and Mara Cercignani[5]

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

INTRODUCTION

Magnetization transfer (MT) imaging is based on the exchange of magnetization between protons in tissue water and those bound to macromolecules. Quantitative MT (qMT) [1] is an extension of MT imaging which attempts to quantify the physical properties that govern the MT process, including the relaxation rates of the pools, the exchange rate, and the relative size of the macromolecular pool. In particular, widespread reductions of the forward exchange rate, RM_{0B}, were recently reported in the cortex of patients with Alzheimer's disease (AD) [2]. One of the interpretations of these findings is that they might reflect metabolic changes preceding macroscopic tissue loss. Aim of this study was to evaluate the sensitivity of qMT imaging to the subtle tissue changes expected in subjects with amnestic Mild Cognitive Impairment (aMCI), a condition considered as a prodromal stage of AD. To this purpose, a multimodal image analysis was used to take into account grey matter (GM) atrophy.

METHODS

We recruited 34 patients diagnosed with probable AD [F/M=23/11; mean (standard deviation, SD) age=70.3 (6.3) years] according to NINCDS-ADRDA consensus criteria [3], and 18 subjects with single-domain amnesic MCI [4] [F/M; 5/13; mean (SD) age=68.6 (9.9)]. Eighteen healthy subjects (HS) were recruited as controls [F/M ratio=7/11; mean (SD) age=66.9 (6.9) years].

All subjects underwent a neuropsychological examination and an MRI acquisition at 3.0T. The MRI session included for every subject: (1) a Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR= 1338 ms, TE= 2.4 ms, Matrix= 256 x 224, n. slices= 176, thick. 1 mm); (2) a series of 12 MT-weighted 3D FLASH sequences (TR= 35 ms, TE= 7.4, flip angle= 7°) with various combinations of amplitude and offset frequency of the MT pulse, optimised according to [5]; (3) three 3D FLASH sequences with variable flip angle for T1 mapping [6]; (4) three 3D FLASH sequences with near-180° flip angles for B_1 mapping [7]. We used the same image analysis pipeline described in [2]. In brief, the MDEFTs were first processed according to the voxel-based morphometry procedure in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/), including normalization, segmentation, and "modulation" (i.e. multiplication by the local Jacobian determinant of the normalization transformation) to yield maps of GM volume in MNI space. Images from sequences (2)-(4) were used to compute the qMT parameters on a voxel-by-voxel basis [8]: T_1 and B_1 maps were obtained as described in [6] and [7], respectively; then, we fitted Ramani's model of MT [9] to the data of sequence (2) to compute maps of R_A, F, T_{2B}, and RM_{0B} (where R_A is the longitudinal relaxation rate of the liquid pool, F= M_{0B}/M_{0A}, is the relative size of the macromolecular pool, RM_{0B} is the forward exchange rate, and R_B is the longitudinal relaxation rate of the macromolecular pool and is fixed at 1 s^{-1}). The largest flip angle scan from sequence (3) was used to compute the transformation for qMT space to MNI space, which was then applied to all qMT parametric maps. qMT and GM volume maps were both smoothed with a 6 mm Gaussian kernel. Normalized and smoothed RM_{0B}, F and T_{2B} maps were compared between groups, using the Biological Parametric Mapping (BPM [10]), an SPM toolbox that permits the use of three dimensional images as nuisance regressors in the statistical analysis. Using BPM, we performed an ANCOVA analysis for assessing between group (HS, aMCI, AD) differences in the (warped and smoothed) qMT maps, using gender, years of education and (modulated and smoothed) GM volume map as nuisance regressors, and confining the analysis to the GM tissue.

RESULTS

Consistent with previous findings [2], the only qMT parameter which showed significant ($p<0.05$, FWE cluster level corrected) between-group differences was RM_{0B}. When comparing HS vs AD, RM_{0B} was reduced in AD patients (Fig 1A). These differences were located in the posterior and anterior cingulated gyrus, in left (L) posterior parieto-occipital cortex, in the temporal pole bilaterally, in the insular cortex bilaterally, in L and right (R) hippocampus/parahippocampal gyrus, in L and R thalamus. When comparing aMCI vs AD, RM_{0B} was reduced in AD (Fig 1B), in the L and R posterior parieto-occipital cortex, in L and R hippocampus/parahippocampal gyrus and in L and R thalamus. No other significant results were obtained.
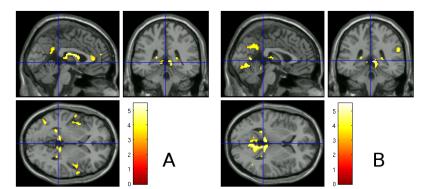

Figure 1. Results of the between-group voxel-based comparison of RM_{0B}. Widespread areas of reduced RM_{0B} were found in patients with AD compared to healthy subjects (**A**), consistent with previous results [2]. Similar results were found when comparing MCI and AD patients (**B**), although the pattern of abnormalities involves less brain areas.

DISCUSSION

Our results confirm that among qMT parameters, RM_{0B} is the most sensitive to AD pathology [2]. Widespread areas of reduced RM_{0B} are found in patients with AD compared to HS, and, less extensively, compared to aMCI patients. We did not find evidence of reduced RM_{0B} in aMCI patients compared to HS. This could reflect the fact that the aMCI patients recruited were all at a very early stage of the disease, being all single-domain aMCI. Therefore the pattern of significant difference we found between aMCI and AD patients indicates the transition between preclinical and clinical AD. Although some of these regions are known to be atrophic in AD patients [11], the multi-modal analysis we ran, adjusting for GM atrophy, suggests that the reduction in RM_{0B} of these areas is not merely the result of GM volume loss.

References

1. Henkelman RM, et al. Magn Reson Med. 1993; 29:759-66; **2.** Giulietti G, et al. Neuroimage. 2011; doi:10.1016/j.neuroimage.2011.09.043; **3.** McKhann G, et al. Neurology. 1984; 3:939-44; **4.** Petersen RC, et al., Arch Neurol 58, 1985-1992; **5.** Cercignani M, et al. Magn Reson Med. 2006; 56:803-10; **6.** Venkatesan R, et al. Magn Reson Med. 1998; 40:592-602; **7.** Dowell N, et al. Magn Reson Med. 2007; 58:622-30; **8.** Cercignani M, et al. NMR Biomed. 2009; 22(6):646-53; **9.** Ramani A, et al. Magn. Reson. Imaging. 2002; 20(10) 721-73; **10.** Casanova R, et al. Neuroimage 2007; 34, 137–143; **11.** Serra L, et al. J Alzheimer D. 2010; 19:147-159.