Joint analysis of structural and quantitative magnetization transfer MRI for classification of Alzheimer's disease and normal aging

G. Giulietti[1], M. Bozzali[1], V. Figura[1], R. Perri[2], C. Marra[3], F. Giubilei[4], and M. Cercignani[1]
[1]Neuroimaging Laboratory, Santa Lucia Foundation, Rome, Italy, [2]Department of Clinical and Behavioural Neurology, Santa Lucia Foundation, Rome, Italy, [3]Institute of Neurology, Cattolica University, Rome, Italy, [4]Department of Neurology, Sapienza University, Rome, Italy

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. These parameters deliver information closely related to biological changes of white matter (WM) and grey matter (GM), and are therefore of potential interest in several neurological disorders. In particular, preliminary studies suggest that qMT might provide complementary information to that offered by other MRI techniques in the characterisation of neurodegenerative diseases, such as Alzheimer's disease (AD) [2, 3]. The results reported in these papers, however, were obtained using a region-of-interest approach, and thus required an a priori hypothesis on the location of the structural changes.
Aim of this study was 1) to extend the assessment of qMT parameters in patients with AD to the whole brain using a voxel-wise approach and 2) to determine the joint contribution of GM regional atrophy and qMT for the classification of AD in a cross-sectional study using a multimodality MRI processing.

METHODS

We recruited 19 patients diagnosed with probable AD [F/M=10/9; mean (standard deviation, SD) age=70.0 (7.7) years] according to NINCDS-ADRDA consensus criteria [4] and 11 healthy subjects (HS) as controls [F/M ratio=4/7; mean (SD) age=63.9 (9.5) 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].
The MDEFTs were first processed according to the voxel-based morphometry procedure in SPM8, 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. GM and qMT maps were smoothed with a 6 mm Gaussian kernel. Normalized and smoothed RM_{0B}, F and T_{2B} maps were separately compared between groups (AD vs HS), adjusting for age and gender. Only the maps that showed significant between-group differences (significant qMT maps) were retained for further analysis. Next, in order to differentiate between the contribution of GM atrophy and qMT parameters to the classification in AD or HS categories, we performed a voxel-wise logistic regression analysis, using GM and significant qMT maps as predictor variables, and diagnosis (either AD or HS) as the outcome.

RESULTS

When comparing each of the qMT parametric maps between AD patients and HS, the only parameter which showed significant ($p<0.05$, FWE corrected) differences was RM_{0B}. RM_{0B} was reduced in the posterior cingulated gyrus, and in the posterior parietal cortex, bilaterally, of AD patients compared to HS (Fig1, in yellow). As explained in the Methods, RM_{0B} was therefore the only qMT parameter included in the logistic regression. Several areas of reduced GM volume (red in Fig 1) and reduced RM_{0B} (blue in Fig 1) were found to be significantly ($p<0.005$) predictive of AD diagnosis using logistic regression. The areas where a reduction of GM volume was significantly predictive were mainly subcortical (left (L) and right (R) putamen, L and R pallidus, R thalamus), while the areas where a reduction of RM_{0B} was significantly predictive were mainly cortical, including L and R hippocampus/parahippocampal gyrus, L and R posterior cingulate gyrus, L and R parietal cortex.

DISCUSSION

This paper attempts for the first time a whole-brain quantification of qMT parameters in patients with AD. Our results indicate that among qMT parameters, RM_{0B} is the most sensitive to AD pathology. RM_{0B} was found to be significantly predictive of AD diagnosis in the hipoccampal/parahippocampal areas, in the posterior cingulate, and in the posterior parietal cortex. Although some of these regions are known to be atrophic in AD patients [10], the multivariate analysis we ran including GM maps suggests that a reduction in RM_{0B} of these areas is more predictive of AD status than a reduction of GM volume. Interestingly, this pattern of reduced RM_{0B} includes most of the areas typically identified as part of the so-called default-mode network [11]. Among these, the posterior cingulate/precuneus and the inferior parietal gyrus are typically characterized by reduced metabolism as assessed by positron emission tomography (PET) in AD [12]. An intriguing interpretation of our results is that RM_{0B} might therefore reflect, at least partially, through the measurement of the efficiency of MT exchange, some metabolic information. Further investigations are needed to clarify this issue.

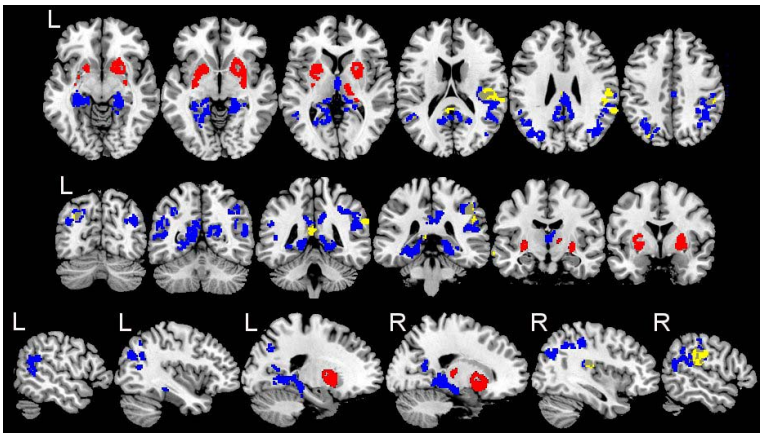

Figure 1. Axial, coronal and sagittal views of significance maps ($p<0.005$, uncorrected for multiple comparisons) of AD vs HS classification power of GM density (in red) and RM_{0B} (in blue). A decrease of both, GM volume in the red regions and RM_{0B} in the blue regions, increases the probability of AD diagnosis. The ANOVA significance map ($p<0.05$, FWE corrected), for the comparison RM_{0B} (AD) < RM_{0B} (HS), is shown in transparent yellow.

References

1. Henkelman RM, et al. Magn Reson Med. 1993; 29:759-66 **2.** Kiefer C, et al. Neuroimage. 2009; 48(4):657-67 **3.** Ridha BH, et al. Radiology. 2007; 244(3):832-7 **4.** McKhann G, et al. Neurology. 1984; 3:939-44. **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.** Serra L, et al. J Alzheimer D. 2010; 19:147-159 **11.** Greicius MD, et al. Proc Natl Acad Sci U S A. 2004; 101(13):4637-42 **12**.Minoshima S, et al. Ann Neurol. 1997; 42:85-94.