Quantitative magnetization transfer: a pilot study in Alzheimer's disease

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Introduction: Magnetization transfer (MT) relies upon the exchange of free protons and those bound to macromolecular structures. Because of this, MT measurements reflect the local chemical and biophysical environment of macromolecules, and so may allow detection and quantification of changes in the histological composition of brain tissue in vivo. Quantitative MT (qMT) [1-3]allows a number of fundamental parameters to be assessed, which may be pathologically specific. Alzheimer's disease (AD) is characterised by neuronal loss, gliosis and deposition of extracellular amyloid plaques and intracellular neurofibrillary tangles. In particular, the entorhinal cortex and hippocampal formation (HF) are selectively involved early in the disease process. This pilot study investigated changes in qMT parameters in the HF in AD patients compared with unaffected elderly controls.

Subjects and methods: Seven patients with a clinical diagnosis of probable AD according to the NINCDS/ADRDA criteria and seven unaffected controls were recruited into the study. Mini-mental state examination (MMSE) was performed as an approximate measure of severity. Subjects were scanned on a 1.5 Tesla MRI system according to the method of Davies et al [3]. A 2D spoiled gradient echo sequence was used with the following parameters: TR/TE= 1140/12 ms, excitation flip angle= 25°, matrix size = 128x256, number of excitations = 0.75, i.e partial filling of *k* space, FOV = 24x18 cm, slice thickness = 5 mm, MT pulse repetition time (TR')= 41 ms. Ten separate measurements were made at differing MT pulse offsets and amplitudes, giving ten unique MT weightings. qMT scanning time was approximately 15 minutes. 28 slices were acquired giving whole brain coverage. T_1 maps were not acquired.

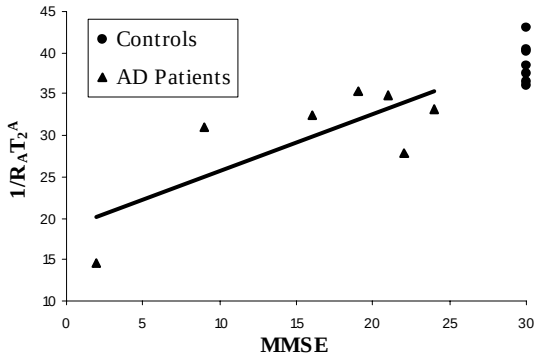
Left and right HFs were traced in the axial view using the semi-automated DispImage package (Plummer, Dept of Medical Physics and Bioengineering, University College London); these regions of interest were placed on each of the 10 differently weighted data sets. The model defined by Henkelman et al[1] and modified by Ramani et al[2] was used with a Gaussian lineshape for the bound protons. This model was used to produce estimates of four qMT parameters: gM_o^A where g is a scanner dependent scaling factor and M_0^A is the magnetisation of the free pool, $1/R_AT_2^A$ which is the ratio of the relaxation times of the free proton pool, $f_b/R_A(1-f_b)$ where f_b is the bound proton fraction and R_A is $1/T_1$ of the free proton pool, and T_2^B, the transverse relaxation time of the bound pool. The median value for each parameter was calculated in each HF. In each subject, the average of right and left HF values was calculated. Patient and control groups were compared using either χ^2 or Mann Whitney U statistics as appropriate.

Results: Age, sex and MMSE characteristics of patient and control groups are shown in table 1. There were no statistically significant differences between AD patients and controls with regards to gM_o^A, $f_b/R_A(1-f_b)$ and T_2^B (Table 1). HF $1/R_AT_2^A$ was significantly lower in the patient group (P = 0.002). In the patient group, there was a positive correlation between $1/R_AT_2^A$ and MMSE (r= 0.76) (figure 1).

Table 1: Age, sex and MMSE characteristics and qMT parameters of AD patient and control groups

	Controls (n=7)	AD patients (n=7)	P value
Age (mean (SD))	69.3 (11.2)	64 (6.5)	0.3
Sex (M:F) ratio	6:1	3:4	0.09
MMSE (mean (SD))	30 (0)	16 (8)	0.0006
gM_o^A (mean (SD))	421 (27)	435 (52)	0.41
$1/R_AT_2^A$ (mean (SD))	39 (2)	30 (7)	0.002
$f_b/R_A(1-f_b)$ (mean (SD))/s	0.098 (0.005)	0.096 (0.005)	0.56
T_2^B (mean (SD))/μs	17.2 (0.7)	17.0 (0.8)	0.75

Figure 1: Mean HF $1/R_AT_2^A$ versus MMSE



Conclusion: This pilot study is the first application of qMT imaging to AD patients with mild to severe dementia. Although further investigation of qMT parameters in a larger patient sample is required, these results suggest that in AD, $1/R_AT_2^A$ may be reduced in the hippocampus, a structure preferentially involved in AD. Most qMT parameters did not seem to be affected by AD. The reduction in $1/R_AT_2^A$ may be due to a lengthening of T_2^A due to membrane breakdown and increase in free water or a decrease in T_1^A (=$1/R_A$). This is probably less likely as pathologies such as gliosis tend to increase T_1 [4]. Direct measurement of T_2^A and comparison with qMT parameters in a larger patient sample is planned.

References:

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3. Davies GR, et al. Mult Scler 2003; 9(3):246-249.
4. Barnes D, et al. Brain 1988; 111 (Pt 1):83-94.