Histogram analysis of the macromolecular proton fraction and bound pool T_2 in multiple sclerosis

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Introduction The magnetization transfer ratio (MTR) correlates with axonal and myelin density (1) and therefore is useful in the study of multiple sclerosis (MS). This study used a model for magnetization transfer (MT) to estimate two underlying parameters (the macromolecular proton fraction (*f*) and the macromolecular T_2 (T_{2b})). The model is based on that of Henkelman et al(2) and has been adapted (3,4) to allow estimation of MT parameters in human subjects. Similar techniques have also been developed by Sled and Pike and Yanykh(5,6). Although results from small regions of interest (ROI) have been reported(7), we now present data from *f* and T_{2b} normal appearing gray and white matter maps, which provide a global but tissue specific measure.

Methods Fifty eight clinically definite MS patients (36 female, 22 male, mean age 47, median expanded disability status scale (EDSS) score 3.0, range 1.0-7.5) and 27 healthy controls (13 female, 14 male, mean age 35) were studied (using a 1.5 Tesla Signa) .Three sequences were acquired in all subjects. 1)A dual echo fast spin echo sequence (TR 2000ms, TEs 19/95ms, 28 contiguous 5mm axial slices covering the whole brain. 2)A MT sequence consisting of a MT pulse (duration 14.6ms, interval between the centers of successive MT pulses 41ms) applied before each slice of a 2D spoiled gradient echo sequence (TR 1180ms, TE 12ms, excitation flip angle 25^o, 0.75 NEX (ie partial k-space acquisition), field of view (FOV) 24x18cm^2 and acquisition matrix 256x128, reconstructed as 256x256 over a 24x24cm^2 FOV, slice thickness 5mm). Ten separate measurements each consisting of 28 contiguous oblique axial slices covering the whole brain were made at differing MT pulse offsets and amplitudes (4). 3) PD and T_1 weighted gradient echo data sets permitting the calculation of T_1 relaxation time(8). Total scan time was 1 hour. The FSE images were registered to the first MT data set (using the AIR package(9)) while the T_1 map and other 9 MT data sets were also registered to this MT dataset using mutual information registration (4). Lesions were then contoured on the FSE data set with DispImage (Plummer, UCL). As previously described (4), the model was fitted on a pixel by pixel basis to the signal intensities from the 10 MT images using a least squares technique based on a Numerical Algorithms Group routine. This allowed for the generation of *f* and T_{2b} maps. A Gaussian line shape was assumed for the absorption line shape of the bound pool. The first MT dataset was used in SPM99 to create white matter (WM), gray matter (GM) and CSF probability maps and whole brain masks were then generated in SPM using the WM and GM probability outputs. These masks were used to remove non-brain parenchyma from the *f* and T_{2b} maps. A maximum likelihood algorithm utilising the three probability maps was then used to separate GM and WM segments in the *f* and T_{2b} maps. Lesions were set to zero to leave only normal-appearing white and gray matter (NAWM and NAGM). These tissue segments were subjected to a single pixel erosion of inner and outer voxels to minimize partial volume voxels. Data from lesion ROIs were also placed on to the T_1 map and 10 MT data sets permitting lesion *f* and T_{2b} to be estimated. Mean values for *f* and T_{2b} from NAWM, NAGM and lesions were compared between subject groups allowing for age and gender effects (using linear modeling - SPSS11.0). The relationships between parameters were assessed with Spearman's rank correlation co-efficient (r_s)

Results Mean *f* values from NAWM, NAGM and lesions were significantly lower in MS patients than controls. For the various tissues, the mean *f* and standard deviations (in brackets) were: NAWM *f:* 12.9% (1.1%) vs 14.2% (0.7%) ($p < 0.001$); NAGM *f*: 8.4% (0.6%) vs 8.9% (0.5%) ($p = 0.008$); Lesion *f* (compared to control WM): 9.9% (1.0%) vs 14.2% (0.7%) ($p < 0.001$). T_{2b} was significantly lower in lesions in comparison to control WM: 17.1 μs (0.5 μs) vs 18.4 μs (0.2 μs) ($p < 0.001$). No difference was seen between NAWM T_{2b} and control WM T_{2b} or between NAGM T_{2b} and control GM $T_{2b.}$ In MS, T_{2b} and *f* were *inversely* correlated in NAWM ($r_s = -0.44$, $p = 0.001$) and NAGM ($r_s = -0.39$, $p = 0.003$). In controls T_{2b} and *f* were *inversely* correlated in NAGM only ($r_s = -0.47$, $p = 0.01$). NAGM T_{2b} in MS was inversely correlated with the EDSS ($r_s = -0.31$, $p = 0.02$).

Conclusions *f* shows widespread abnormality and is reduced in NAWM, NAGM and lesions whereas T_{2b} is only reduced in lesions. The inverse relationship between *f* and T_{2b} in normal appearing brain tissue confirms the earlier ROI analysis(7) and appears to be present in controls and MS patients alike. This might occur as result of a slight variation in brain tissue free water content, with low *f* and high T_{2b} corresponding to high free water content. If true, any *decrease* in T_{2b} (eg in lesions) may be independent of free water effects (such as edema) and therefore could be specific for changes in tissue structure (presumably demyelination, axonal loss and gliosis). This could be why NAGM T_{2b} (as opposed to NAGM *f*) correlates with the EDSS. However further work, including histopathologic studies, are now needed to confirm these findings

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