Magnetization Transfer Imaging of Individual Beta-Amyloid Plaques in Alzheimer's Disease

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Introduction: Our previous research (1,2) into further understanding the transverse relaxation and image contrast associated with beta-amyloid (Aβ) plaques in Alzheimer's disease (AD) illuminated that transverse T_2* relaxation and contrast seen in T_2* weighted images of Aβ plaques is associated with both plaque morphology and iron content. This data indicated that iron content and plaque composition synergistically cause the additive effect upon transverse relaxation. Iron content, while a factor in the MR imaging of plaques, alone is not responsible for the hypo-intensities seen on the MR images and that the dense fibrillar nature of the Aβ plaques has a major role in shortening of the transverse relaxation in human AD tissue. The fibrillar organization and hydrophobic / hydrophilic polypeptide regions which comprise the beta-amyloid plaques presents an ideal setting for hydration water protons to bond to the surface of the Aβ macromolecule architecture via dipole-dipole interactions. Using magnetization transfer (MT) imaging it should be possible to pre-saturate the Aβ bound protons with an off-resonant frequency-selective rf pulse within the broad spectral line of the bound proton pool thus augmenting the relaxation of free water. Previous research has shown that quantitative MT ratio (MTR) differences are present in AD brain regions compared to normal controls (3,4). The goal of this research was to build upon previous histological MR imaging to quantitatively measure MT associated with Aβ plaques. To our knowledge, this is the first demonstration of quantitative MT measurements associated with individual Aβ plaques. Detailed histological MR examination using ultra-high resolution micro-MR imaging techniques in comparison to traditional histology methods of human AD tissue samples are described.

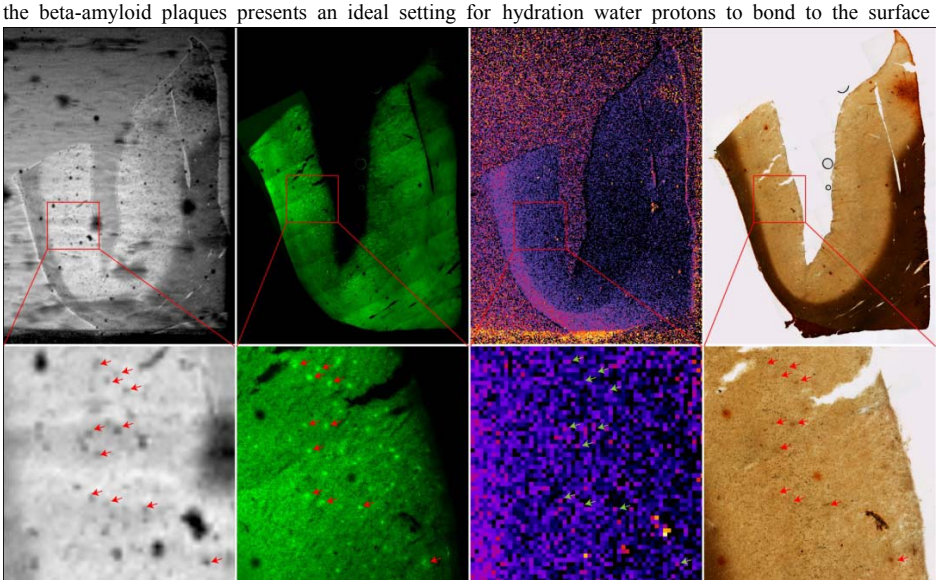

Figure 1: T_2* weighted MR images (far left), Thioflavin-S stain (middle left), Δf=15kHZ MTR parametric map (middle right) and Perl's stain (far right) same human AD tissue samples. All images have the same region expanded in the bottom row. The MR and histology stains show the characteristic MR hypo-intensities, fluorescence and focal iron associated with the Aβ plaques. Beta-amyloid plaques in these enlarged images are emphasized with red arrows. The MTR parametric map shows focal regions of high MTR associated with Aβ plaques (green arrows) whose location directly compares to the T_2* and histological data.

Methods: Entorhinal cortex brain tissue samples from clinically and histologically determined AD subjects (N=5) were used throughout the study. Tissue samples fixed with paraformaldehyde and cryogenically protected with sucrose were cut at 60μm using a cryostat, rinsed with in phosphate buffered saline (PBS) to eliminate any residual fixative and sucrose and prepared for micro-imaging within the 7.0 T histological coil (1, 2) on a Bruker MedSpec 7.0T system. For relaxation MR imaging an eight echo T_2* MGE sequence and eight echo T_2 MSME scans were utilized with a matrix of 512^2 and a final pixel resolution of 45μm x 45μm in the through-plane direction. MT-weighted images were acquired using a set of five gradient echo FLASH sequences with Gaussian modulated pre-saturation pulses located at frequency offsets Δf=1.0, 2.5, 5.0, 10.0 and 15.0 kHz with respect to the central 1H Larmor frequency. Quantitative parametetric MT ratio (MTR) maps were calculated by comparing the MT images acquired at different offset frequencies ($M_{\Delta f}$) to the data without pre-saturation (M_0): $MTR=100*(M_0-M_{\Delta f})/M_0$. Data was prepared and calculated using in-house IDL and Matlab scripts as well as NIH ImageJ software. Following histological MR imaging, the slices were co-stained with Thioflavin-S for Aβ plaque detection and a Perl's – Diaminobenzene stain for ferric iron. Regions of interest (RIO) for Aβ plaques, surrounding gray matter, and white matter were defined on the T_2* weighted echo-summated MGE images using the histological stains for positive plaque verification. These RIO's where imported and overlaid on the MTR parametric map data and detailed MTR's were quantified for individual plaques and all other RIO's.

Results: Figure 1 shows a T_2* weighted MR images (far left), Thioflavin-S stain (middle left), Δf=15kHZ MTR parametric map (middle right) and Perl's stain (far right) same human AD tissue samples. The T_2* MR images show characteristic MR hypo-intensities associated with Aβ plaques and iron deposition, whose location is verified with the histological stains. The parametric MTR images show regions with a high concentration of macromolecular bond protons as bright on the heat map parametric maps. The method is confirmed with the high MTR associated with white matter tracks due to the high myelin lipid content in these regions. Individual plaques are able to be resolved as single or small groupings of 45μm x 45μm voxels on the MTR parametric images. Figure 2 shows a graph of the MTR associated with the Aβ individual plaques, gray matter and white matter ROI's. The Aβ plaque MTR is higher than the surrounding gray matter and approached the MTR value of white matter, demonstrating that tightly bound protons are present on the surface of the Aβ macromolecule architecture.

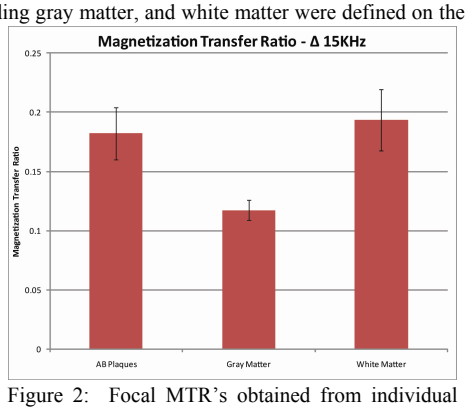

Figure 2: Focal MTR's obtained from individual Aβ plaques, gray matter and white RIO's. The individual Aβ plaques have a higher MTR compared to the surrounding gray matter, approaching that of white matter.

Discussion: Our previous research illustrated that transverse T_2* MR contrast seen in images of Aβ plaques is synergistically associated with both plaque morphology and iron content. It was not clear how the Aβ plaque morphology caused the associated MR hypo-intensities which guided our investigation further. MTR imaging of individual plaques was the next feasible method to tease apart this relationship. To our knowledge, this data represents the first magnetization transfer imaging of individual Aβ plaques and builds upon previous MT research showing that regions known to contain high Aβ plaque loads have different MTR's from surrounding non-plaque burdened regions. The macromolecular architecture of the Aβ plaques is ideal for hydration water protons to bond to the component Aβ fibrils via dipole-dipole interactions. The data represents a required step forward in understanding the cause of the transverse relaxation associated with the structure Aβ plaques and helps provide a foundation for the future high resolution Aβ plaque clinical imaging.

References: 1 – Meadowcroft *et al*. Mag. Reson. Med. 2007; 57(5): 835-841, 2 – Meadowcroft *et al*. JMRI 2009; 29(5): 997-1007, 3 – Kiefer *et al*. NeuroImage 48 (2009) 657–667, 4 – Ridha *et al*. Radiology 2007; 244(3): 832-837.