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

M. D. Meadowcroft, Z. G. Herse, J. R. Connor, and Q. X. Yang

1Radiology - Center for NMR Research, Pennsylvania State University - College of Medicine, Hershey, PA, United States, 2DMCP - Neuroimaging, Bristol-Myers Squibb, Wallingford, CT, United States, 3Neurosurgery, Pennsylvania State University - College of Medicine, Hershey, PA, United States

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 synergetically 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 macroarchitecture 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.

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 512² 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 parametric MT ratio (MTR) maps were calculated by comparing the MT images with the MTR parametric map using a $Δf=15$ KHz 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.

Discussion: Our previous research illustrated that transverse $T_2^*$ MR contrast seen in images of Aβ plaques is synergetically 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. MT 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 macroarchitectural organization 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.


Figure 1: $T_2^*$ weighted MR images (far left), Thioflavin-S stain (middle left), $Δf=15$ KHz 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.

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.