Visualizing Amyloidal Deposition in a Transgenic Mouse by MRI

A. Borthakur[1], K. Uryu[2], M. Corbo[1], A. J. Wheaton[1], E. R. Melhem[1], J. Q. Trojanowski[2], V. M-Y. Lee[2], R. Reddy[1]

[1]Radiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Pathology & Lab Medicine, University of Pennsylvania, Philadelphia, PA, United States

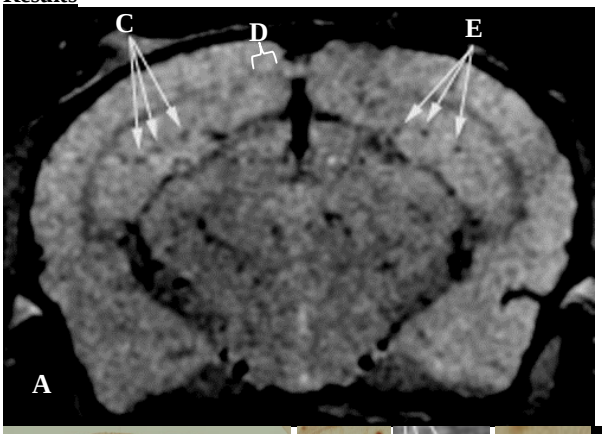
Introduction

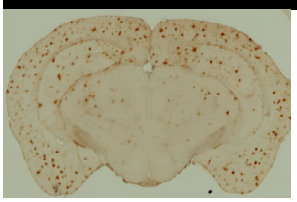
Alzheimer's disease (AD) is the most common form of dementia in the elderly (1). Classic symptoms of the disease include memory loss, confusion and neuropathological features such as neurofibrillary tangles (NFTs) formed by paired helical filaments composed of tau protein and senile plaques (SP) resulting from insoluble Amyloid-β (Aβ) deposits as well as neuron loss in the limbic and neocortical regions. Results from recent experiments have detected plaques in human brain tissue specimens with high resolution T_2*-weighted MRI (1). There are some studies of plaque detection using exogenous contrast agents (2, 3). However, to the best of our knowledge, there are no studies demonstrating plaques in live animal models without using exogenous contrast agents. $T_{1\rho}$, or "T-1-rho", the spin lattice relaxation time constant in the rotating frame, determines the decay of the transverse magnetization in the presence of a spin-lock radio-frequency field. Whereas quantifying T_2* with MRI can be prone to errors from susceptibility-induced signal losses if not performed carefully and the T_2-weighted MR signal is degraded by diffusion, $T_{1\rho}$-weighted MR images are not affected by any such losses. Therefore, quantitative $T_{1\rho}$ MRI is an attractive proposition for the detection and quantification of Aβ deposits. We previously demonstrated that $T_{1\rho}$ relaxation rate is increased in transgenic mouse brain in regions containing plaques (4). In this work, we optimized the pulse sequence parameters that resulted in thinner slice sections of 130μm with unique delineation of the Aβ plaque deposits.

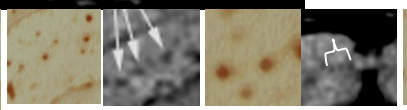
Materials and Methods

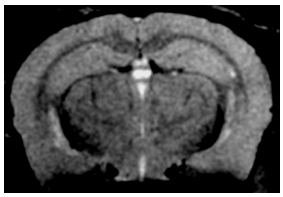
Two APP/PS1 tg mice (both 18-month old) and two age-matched control mice were anesthetized with ketamine/acepromazine. These mice were then mounted on a bed and connected to an isoflurane inhalation anesthesia apparatus. The position of each slice relative to the anterior end of the brain was noted and extreme care was taken to ensure that the head and body of the animal lay flat on the bed to facilitate subsequent matching with histological sections. The bed was placed into a home-built, 3cm diameter birdcage coil and the mouse brain was imaged using a 4.7T horizontal-bore animal imaging spectrometer connected to a Varian console. Axial $T_{1\rho}$-weighted MR images were obtained with a three-pulse spin-locking sequence pre-encoded to a gradient-echo readout sequence. Imaging parameters were TE/TR=2ms/500ms, flip angle=45°, FOV=2cmx2cm, thickness=130μm, matrix size=256x256, in-plane pixel size of 78μm x 78μm, and the spin-lock time (TSL) was 10ms and spin-lock field (γB_1) was 500Hz. Following imaging, the animals were decapitated, and the brains were fixed in 10% neutral buffered formalin overnight. The brains were embedded in paraffin. Several 10μm sections were then immuno-stained with Aβ specific antibody (4G8) using 3,3'-diaminobenzidine for visualization (5) and digital images were obtained with a digital slide scanner. Four consecutive histological sections were selected and manually overlaid on each other in Photoshop to generate a 40μm-thick section for a more meaningful comparison with the corresponding MR image.

Results









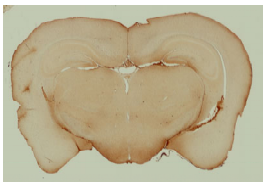


Figure 1: $T_{1\rho}$-weighted MR image of the APP/PS1 mouse brain (**A**) shows hypo-intense regions indicated by the arrows. The corresponding immuno-stained histology section (**B**) created by combining four 10μm-thick sections shows a prolific distribution of Aβ deposition. The magnified regions (**C**-**E**) correspond to regions indicated by the arrows in figure **A** show identical clusters of Aβ deposits in the hippocampus and cortex in both the histological section as well as the MR image. The $T_{1\rho}$-weighted MR image of an age-matched control (**F**) and corresponding histology (**G**) failed to show plaques in the same regions.

Analysis of the MR images determined that most of the plaques were visible in hippocampus. This was expected since the imaging parameters were optimized for contrast in this region as it exhibits the most prolific distribution of Aβ plaques in humans. We are currently developing strategies for optimizing contrast in the cortex to better visualize the plaques in those regions.

Conclusion

We have demonstrated that high-resolution $T_{1\rho}$-weighted MRI can visualize Aβ plaque deposition in a transgenic mouse brain *in vivo*. Improvements in signal-to-noise from a higher field magnet are being explored. Increased SNR will permit acquisition of thinner slice sections in the MRI and reduce partial-volume effects and therefore improve delineation of plaques. Further, 3D rendering algorithms of histological sections are being developed for more accurate comparison of histological sections and MR images.

Acknowledgments:

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References:

1. Benveniste, H., *et al. Proc Natl Acad Sci U S A* **96**: 14079-14084, 1999.
2. Poduslo, J.F., *et al. Neurobiol Dis* **11**: 315-329, 2002.
3. Wadghiri, Y.Z., *et al. Magn Reson Med* **50**: 293-302, 2003.
4. Borthakur, A., *et al. Proc Intl Soc Magn Reson Med*, 2039, 2003.
5. Skovronsky, D.M., *et al. Proc Natl Acad Sci U S A* **97**: 7609-7614, 2000.