In Vivo T_{1ρ}-weighted MRI of Amyloid Transgenic Mouse Model of Alzheimer’s Disease

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Synopsis
Early in its disease progression, Alzheimer’s disease (AD) is characterized by the formation of amyloid (i.e. senile) plaques, which are extra-cellular deposits of insoluble amyloid-β peptide. Currently, there is a dearth of in vivo imaging techniques for the early detection of AD plaques. In previous studies, T_{1ρ}-weighted (or spin-lock) MRI has shown some promise in generating tissue contrast based on variations in protein content. Here, we demonstrate the feasibility of T_{1ρ}-weighted MRI in generating selective contrast in Aβ plaques in the brains of transgenic mouse models of the AD amyloidosis (Tg2575) in vivo.

Introduction
The early detection of Alzheimer’s disease presents a major challenge to modern imaging technologies. The evaluation of potential new therapies and longitudinal monitoring of disease progression requires objective, quantitative, non-invasive imaging strategies that are sensitive to biochemical changes in brain tissue afflicted with AD. In this context, T_{1ρ}-weighted (or spin-lock) MRI provides a novel modality for generating tissue contrast. T_{1ρ}, or “T-1-rho”, is the spin lattice relaxation time constant in the rotating frame. T_{1ρ} MRI contrast is generated during the decay of the transverse magnetization in the presence of a “spin-lock” RF field. T_{1ρ} MRI has been applied to study tumors in the brain (1) in which there is a high correlation between T_{1ρ}-weighted and magnetization-transfer, or MT-weighted, MR images. This suggests a link between T_{1ρ}-weighted image contrast and the macromolecular composition of tissue. Similarly, the macromolecular changes in AD are expected to alter bulk water MR relaxation times and may be indirectly quantified by spatially mapping the T_{1ρ} relaxation times. While there have been in vitro studies on fixed human and animal brain tissue, to the best of our knowledge, there have been no in vivo MRI studies visualizing Aβ plaques. In this work, we present in vivo T_{1ρ}-weighted MRI images of a mouse model of AD, an amyloid transgenic mouse over-expressing a mutated form of human Aβ.

Materials and Methods
Two 6-month old Tg2575xPS1 mice and two age-matched control mice were anesthetized with ketamine/acepromazine. These mice were then mounted on a bed and connected to an isoflurane inhalational anesthesia apparatus. The bed was placed into a home-built, 3cm diameter birdcage coil and the mouse head was imaged using a 4.7T horizontal-bore animal imaging spectrometer connected to a Varian console. Axial T_{1ρ}-weighted MR images were obtained with a three-pulse spin-locking sequence pre-encoded (2) to a gradient-echo readout sequence. Typical imaging parameters were TE/TR=9ms/500ms, flip angle=45°, FOV=2cmx2cm, thickness=0.5mm, matrix size=256x256, the spin-lock field was 500Hz, and the spin-lock time (TSL) was 20ms. Following imaging, the animals were decapitated, and the brains were fixed in 10% neutral buffered formalin overnight. The brains were embedded in paraffin. Several 6µm sections were then immuno-stained with Aβ specific antibody (4G8) using 3,3’-diaminobenzidine for visualization (3) and digital images were obtained with a camera attached to a light microscope.

Results

Conclusion
These preliminary experiments demonstrate that T_{1ρ}-weighted MRI has the potential to visualize Aβ-plaque formations in an animal model of AD. Further work in optimizing imaging parameters is in progress, with the aim of better visualizing this pathology.

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References

Figure 1: T_{1ρ}-weighted MR images of control (A) and Tg2575 (B) mouse brain. A histological section (C) of the Tg2575 mouse in image B shows the location of multiple Aβ plaques (dark brown spots). Images D-F are magnified images of the regions indicated by the squares in A-C, respectively. Areas of low signal (indicated by arrows), representing suspected Aβ deposits, are visible in the Tg2575 mouse (E) and absent in the control (D). Apparent parenchymal atrophy was also evident in the Tg2575 mouse.