Quantitative T2 Mapping in a Niemann-Pick Type C Mouse Model

J. Totenhagen[1], K. Thome[2], C. Howison[3], R. P. Erickson[2], and T. P. Trouard[1,4]

[1]Biomedical Engineering, University of Arizona, Tucson, Arizona, United States, [2]Pediatrics, University of Arizona, Tucson, Arizona, United States, [3]Arizona Research Laboratories, University of Arizona, Tucson, Arizona, United States, [4]Radiology, University of Arizona, Tucson, Arizona, United States

Introduction

Niemann-Pick Type C (NPC) disease is an autosomal recessive neurodegenerative disorder characterized by defective transport of intracellular lipids, resulting in lysosomal accumulation of unesterified cholesterol [1]. No current effective treatments are available, but several therapies have been proposed and investigated in animal models, such as use of the neurosteroid Allopregnanalone [2, 3]. Development of a reliable and quantitative non-invasive imaging technique will be vital in following the progression and response to treatment of NPC disease in both preclinical and clinical evaluations of NPC therapies. Diffusion tensor imaging (DTI) has previously been used to quantitate differences in the fractional anisotropy of NPC diseased brain tissue in both mouse models and human patients [3, 4]. However, DTI experiments in mouse brains take a significant amount of experimental time. In this work we have investigated quantitative T2-mapping for faster evaluation of NPC disease in a mouse model.

Methods

Three types of mice were imaged: a mouse model of NPC disease (BALB/cJ model) which is deficient of the *Npc1* gene in all cells (NPC), a transgenic mouse strain in which a Glial Fibrillary Acidic Protein promoter was used to direct expression of the *Npc1* gene in only glial cells (GFAP), and age-matched wild-type mice with normal *Npc1* gene expression in all cells (WT).

Mice were imaged at approximately 70 days of age using a Bruker Biospec 4.7T instrument with 200 mT/m shielded gradients. All mice were anesthetized with isoflourane and placed into a head holder inside a 25mm LitzCage Quadrature transmit/receive coil (Doty Scientific Inc.) for imaging. Body temperature was monitored with a fiber optic rectal probe and maintained at approximately 37 °C by heated air. T2-weighted datasets were collected with a radial fast spin-echo sequence using the following parameters: ETL=8, TE=15ms, TR=3000ms, 2 averages, 1024 radial views, and 256 sample points per view. A previously published bit-reversal view ordering was implemented to obtain a high variation of signal intensity with view angle, reducing radial streaking [5]. Thirteen contiguous 1mm coronal slices were used to cover the brain for a total scan time of 12:48 (min:sec) per dataset.

Eight images with varying T2 weighting were obtained from a single radial dataset through use of a novel reconstruction method taking advantage of the oversampling of the center of k-space in radial acquisitions [6]. The use of this reconstruction method allowed a reduction in experimental time by requiring a single radial data set to be collected for T2 calculations rather than a separate data set at each TE. Quantitative T2 maps were calculated from the T2-weighted images and a region of interest (ROI) analysis was performed. Regions were drawn on four contiguous T2-weighted coronal slices with MRIcro software (Rorden, 2005), aided by a mouse brain atlas (www.mbl.org). Care was taken to draw generous regions in the areas of the external capsule, corpus callosum, and cingulum while avoiding inclusion of the lateral ventricular spaces. Analysis of the ROIs applied to T2 maps was performed with programs written in MATLAB (Mathworks, Natick, MA). Inverse cumulative histograms were created to illustrate the differences in T2 values in the NPC, GFAP, and WT mice.

Results and Discussion

Coronal T2-weighted images and T2 maps are shown in Fig. 1. Qualitative differences in T2-weighted intensity can be seen in the areas of the corpus callosum, cingulum, and external capsule, as pointed out by arrows. The differences in intensity are likely due to dismyelination in NPC disease [1]. Quantitative results are shown in Fig. 2 from a ROI analysis of T2 values in WT, NPC, and GFAP mice. The T2 values of the ROIs are presented as an inverse cumulative histogram, the ordinate values correspond to the % of ROI pixels above the value on the abscissa. A striking difference is seen in the T2 values of NPC and WT mice, and suggests that quantitative T2 imaging may be a useful tool in future studies of NPC treatments, providing a faster and simpler measurement than DTI. A normalization of T2 values with transgenic modification is also apparent.

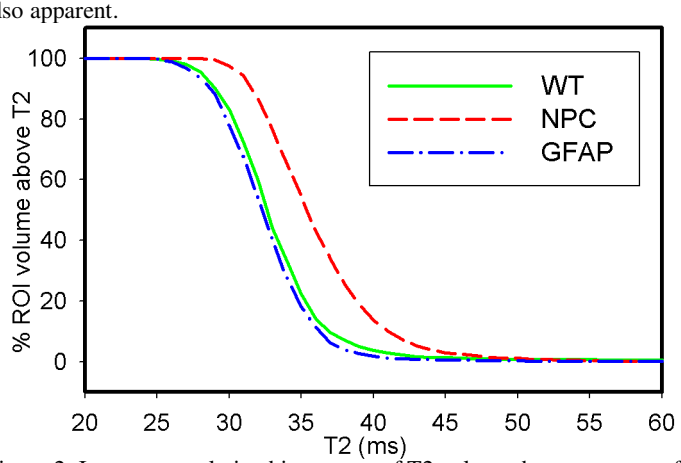

Figure 2. Inverse cumulative histograms of T2 values, the percentage of ROI pixels above a certain T2 value, for WT, NPC, and GFAP mice.

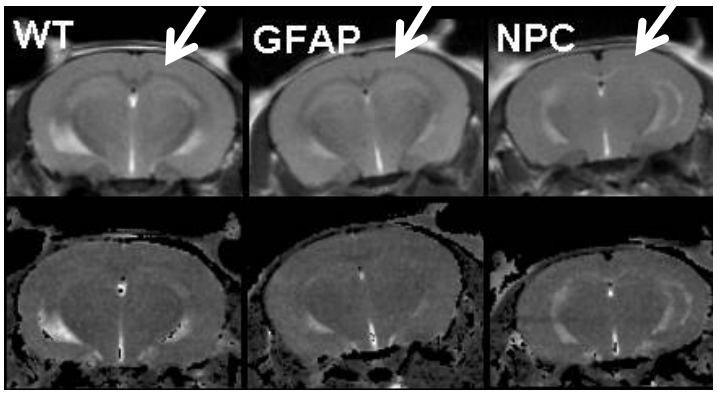

Figure 1. T2 weighted images (top row) and T2 maps (bottom row) of a coronal section of WT, GFAP, and NPC mice. The T2 maps are displayed with a window width of 200, centered at 100 ms.

References

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