Magnetic Resonance Morphometry in a Mouse Model of Niemann Pick Type C Disease

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Introduction

Niemann Pick Type C (NPC) disease is genetic, rare, and fatal. The primary cause of the disease is a defect in the *NPC1* gene, causing dysfunction of the transmembrane protein NPC1, found in lysosomes and late endosomes throughout the body. The lack of NPC1 protein function results in a buildup of cholesterol and glycolipids in cells, leading to progressively worsening symptoms including ataxia, dystonia, dysarthria, dysphagia, and dementia **[1]**. Diagnosis is most often made during childhood with death occurring prior to adulthood. No proven effective treatments or cures are currently available, but several are in development and testing.

The *Npc1*$^{-/-}$ mouse model has a complete lack of functional Npc1 protein, resulting in a phenotype resembling a severe form of human NPC disease. The *Npc1*$^{-/-}$ model has been used in many studies of proposed NPC treatments including cyclodextrins which have been shown to reduce neurological disease symptoms **[2]**. Advancements in high resolution MR imaging of rodent brains has allowed techniques such as tensor based morphometry (TBM) to be applied to preclinical disease studies of neurodegenerative diseases. In this work, high-resolution in vivo images of *Npc1*$^{-/-}$ are analyzed to measure volumes of discrete brain regions with an atlas based approach as well as examine brain atrophy within and across brain regions with a TBM-based analysis.

Methods

High resolution T2-weighted in vivo brain images were obtained from WT and *Npc1*$^{-/-}$ mice at 3, 6, and 9 weeks of age, covering a range from an early presymptomatic disease state to near end stage of the *Npc1*$^{-/-}$ model. A 7T Bruker Biospec system was used for imaging experiments with a 4-channel phased array surface coil and animal bed system with ear bars and bite bar for head fixation. Animals were anesthetized with isoflurane gas and temperature maintained with a circulating heated water system. A 3D fast spin echo sequence was used for data collection with the following parameters:. TR=1800 ms, ETL=8, Echo Spacing=10 ms, TE_{eff}=40 ms, FOV=30 x 17 x 9.6 mm^3, 100µm isotropic resolution, and scan time: 60:08 (min:sec).

Datasets were semi-automatically segmented to isolate the brain from surrounding tissue, and corrected for surface coil signal inhomogeneity using the N4ITK algorithm **[3]**. The SyN image registration algorithm implemented in the advanced normalization tools (ANTS) software package **[4]** was used to register each segmented brain to a labelled MRI in vivo mouse brain atlas **[5]**. The registration to a labeled mouse brain atlas allowed the volume measurement of 20 individual brain structures. Brain templates were created with algorithms included in the ANTS software package using the symmetric normalization (SyN) algorithm. Registering segmented brains to the created templates allows visualization of regional brain volume changes by examining maps of the determinants of the Jacobian matrix of the deformation transformation for each voxel.

Results and Discussion

Example WT and *Npc1*$^{-/-}$ images obtained at 9 weeks of age are shown in Fig. 1. Differences in white matter contrast, ventricle size, and overall brain size and shape are visible in the T2-weighted images, particularly in the areas of the corpus callosum, lateral ventricles, and cerebellum. Results of atlas-based volumetric measurements are shown in Fig. 2 for six brain regions found to differ in size between WT and *Npc1*$^{-/-}$ mice. Fig. 3 illustrates example templates of the WT and *Npc1*$^{-/-}$ brains, with a map of determinant values of the Jacobian matrix of the volume transformation of the *Npc1*$^{-/-}$ template to WT. The determinant map provides visualization of changes in volume within and across brain regions.

Past studies of the *Npc1*$^{-/-}$ mouse model have reported a decrease in overall brain size and cerebellar volume with manual region tracing of ex vivo 2D datasets **[6]**. The current work demonstrates that several brain structures including the cerebellum are reduced in size in the *Npc1*$^{-/-}$ mouse, and can provide additional insight into neurodegenerative status during treatment studies.

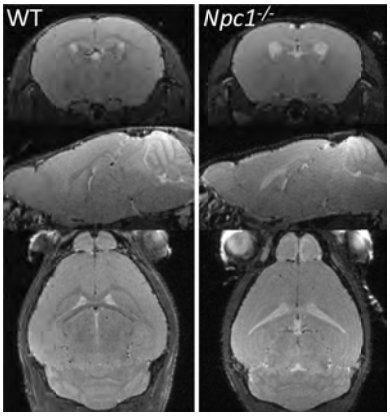

Figure 1. Example in vivo images of WT and *Npc1*$^{-/-}$ mice brains at 9 weeks of age.

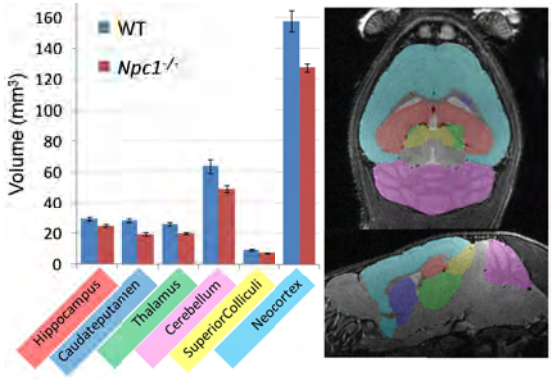

Figure 2. Results of volumetric measurements from six brain regions found to significantly differ in size between WT and *Npc1*$^{-/-}$ mice (P<.001), error bars represent standard deviations.

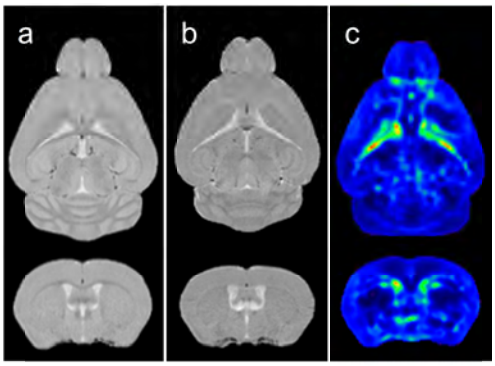

Figure 3. 9 week old WT (a), and *Npc1*$^{-/-}$ (b) templates, a map of local volume expansion/contraction is shown (c), dark blue areas represent areas of brain atrophy in the *Npc1*$^{-/-}$ template relative to WT, green and orange colors mark areas of expansion.

References

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