Major White Matter and Hippocampal Alterations in a Mouse Model of Sanfilippo Syndrome at 7T MRI

Erjun Zhang[1,2], Mahsa Taherzadeh[2,3], Irene Londono[2], Jérémie Fouquet[4], Benjamin De Leener[1,2,5], Alexey V. Pshezhetsky[2,3], Gregory A. Lodygensky[2]

[1]*Institute of Biomedical Engineering, Polytechnique Montreal, Montreal, QC, CA* [2]*CHU Sainte-Justine University Hospital Center, University of Montreal, Montreal, QC, CA* [3]*Department of Anatomy and Cell Biology, McGill University, Montreal, QC, CA*
[4]*Cerebral Imaging Centre, Douglas Research Centre, McGill University, Montreal, QC, CA* [5]*Department of Computer Engineering and Software Engineering, Polytechnique Montreal, Montreal, QC, CA*

Introduction

Sanfilippo syndrome type C is a rare lysosomal storage disorder that leads to progressive neurodegeneration in children. It presents with severe neurological symptoms, including aggressive behavior, hyperactivity, and autistic behavior. Specific treatment for this disorder is not yet available. Sanfilippo syndrome leads to neurodegeneration, chronic progressive neuroinflammation and early death of patients [1] and in a Knockin (KI) mouse model [2].

Problems: But there is less data available regarding white matter integrity and approaches for understanding and monitoring Sanfilippo Syndrome are needed.

Solutions: One promising approach for understanding and monitoring Sanfilippo Syndrome is using imaging biomarkers:

1. Specifically magnetic resonance imaging (MRI) with $T2\star$ mapping
2. Diffusion tensor imaging (DTI)
3. Diffusion Basis Spectrum Imaging (DBSI) [3].

Objectives

To quantify the impacts of Sanfilippo syndrome on mice brain using $T2^*$ mapping and ex vivo DTI and DBSI, focusing on hippocampal and corpus callosum integrity.

Methods

Data acquisition:$7T$ *Bruker* scanner at Cerebral Imaging Centre of The Douglas Research Centre, Montreal, Canada.

Acquisition	TR/TE	Resolution	Other
T2*	$70ms/4ms$	$100 \times 100 \times 200\mu m^3$	9 echoes ($5ms$)
DBSI	$3300ms/32ms$	$0.15 \times 0.15 \times 0.4mm^3$	$0 < b \leq 3000s/mm^2$

Subjects: 10 control mice, 8 mutant mice with Sanfilippo syndrome, on the age of 7 month

Data processing

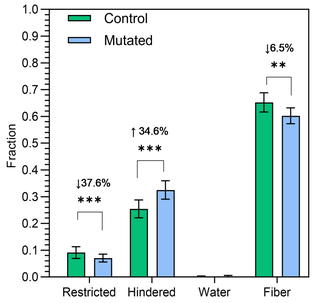
1. Denoising and registration (DTI-TK, DIPY)
2. Reconstruction: DBSI, and DIPY-DTI (non-linear algorithm)
3. Compute T2* maps: A monoexponential fitting, MGE data, qMRLab

Regions of interest: Similar small regions of interest (ROI), manually selected on Corpus callosum (CC) and hippocampal regions CA1 on color-coded fractional anisotropy (FA) maps extract from DTI.

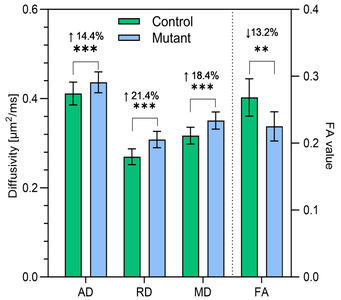
Statistics: Mann-Whitney test ($p < 0.05$) was used on metrics extracted from DTI and DBSI and $T2^*$ between the control and the mutant groups. Notes: $*$ means $p < 0.05$; $**$ means $p < 0.02$; $***$ means $p < 0.01$ in the result figures.

Results

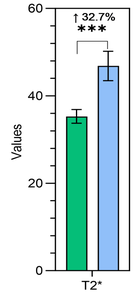
In CA1 of the hippocampus (Figure 1)



(a) DBSI results of CA1



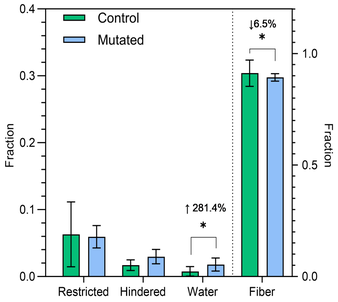
(b) DTI results of CA1



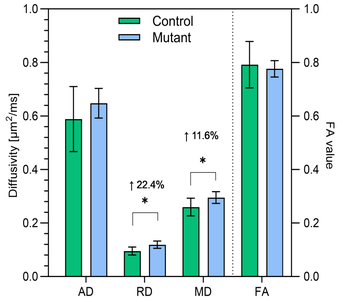
(c) T2* results of CA1

Major microstructural alterations happened both on DTI with increase in Radial, Axial, and Mean diffusivity and a reduction in Fractional anisotropy, Fiber fraction, and restricted diffusivity with an associated increase in Hindered diffusivity. A significant increase in T2* (shown in Fig. 1 (c) and Fig. 3) further confirmed the diffusion results.

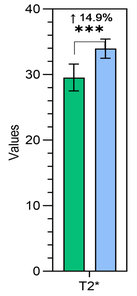
In the corpus callosum (Figure 2)



(a) DBSI results of CC

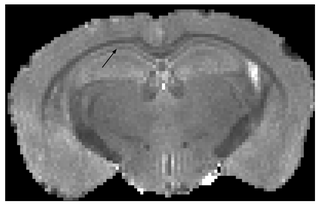


(b) DTI results of CC

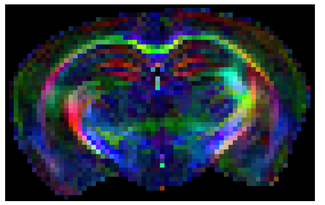


(c) T2* results of CC

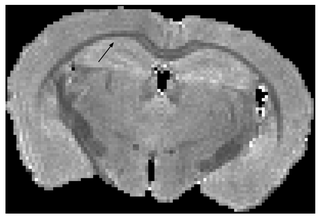
We found compelling signs of white matter injury with significant increases in Radial diffusivity (demyelination), a reduction in Fiber fraction and increase in Water fraction and increase in T2*.



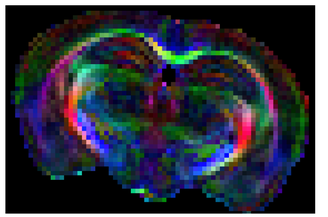
(a) $T2^*$: control



(b) Color-coded of FA map: control



(c) $T2^*$: KI



(d) Color-coded of FA map: KI

Fig. 3: Left column $T2^*$ map, Right: color-encoded FA map. Changes in hippocampal microarchitecture (black arrow) on the $T2^*$ map.

Conclusion

Our data, for the first time, demonstrate that our KI model of Sanfilippo syndrome induces significant white matter injury and visible alteration of hippocampal structure.

We believe these findings will be crucial in establishing non-invasive biomarkers for disease progression and therapeutic response evaluation in future pediatric clinical trials.

References

[1] C Bartsocas and et al. Sanfilippo type C disease: clinical findings in four patients. *Eur. J. Pediatr.*, 130(4), April 1979.

[2] Carla Martins and et al. Neuroinflammation and neurodeg. in mucopolysaccharidosis. *Brain*, 138(Pt 2), February 2015.

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