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

Version: Final; Jan. 13, 2023; Replaced by high-resolution figure on Jan. 17, 2023

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

Background

PMucopolyssacharidosis IIIC (MPSIIIC) or 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. Neurodegeneration and chronic progressive neuroinflammation are well-documented in MPSIIIC patients (Bartsocas et al., 1979) and in a Knockin (KI) mouse model (Martins et al., 2015) but there is less data available regarding white matter integrity. Specific treatment for this disorder is not yet available. One promising approach for understanding and monitoring Sanfilippo Syndrome is the use of imaging biomarkers, specifically magnetic resonance imaging (MRI) with $T2^*$ mapping and diffusion tensor imaging.

Objective

To quantify the impacts of MPSIII on mice brain by $T2^*$ mapping as well as ex vivo DTI and a novel diffusion model: Diffusion Basis Spectrum Imaging (DBSI) (Wang et al., 2011), with a focus on hippocampal and corpus callosum integrity.

Design/Methods

Two groups of 7-month-old mice were chosen and imaged on a preclinical scanner at the Cerebral Imaging Centre of the Douglas University Institute in Montreal, Canada. The control group consisted of four mice; the MPSIIIC group (KI mice) of eight mice. Animals were perfused with PBS followed by 4% paraformaldehyde (PFA) under terminal anesthesia and brains were carefully removed and immersed in PFA for 5 h. Brains were then mounted in a syringe with Fomblin oil for ex vivo MR imaging, using a solenoid coil custom-built to the syringe.

Imaging was carried out on a 7T Bruker MRI scanner. 2D spin-echo sequences with pulsed gradients were used to acquire diffusion-weighted data. It included 1 b0 and 25 b-values ($0 < b \leq 3000 s/mm^2$) with different b-vectors, with field of view $12mm \times 12mm$, resolution $0.15 \times 0.15 \times 0.4mm^3$, and TR/TE: $3300ms/32ms$. $T2^*$ was acquired with a 3D multi-echo gradient echo acquisition (MGE) with field of view $12mm \times 12mm$, resolution $100 \times 100 \times 200\mu m^3$, TR/TE: $70ms/4ms$, echo spacing $5ms$, and number of echoes 9.

Diffusion data was first processed by denoising and registration (DTI-TK). Then, DBSI and DIPY-DTI (non-linear algorithm) were used for reconstruction. Regions of interest (ROI) were manually selected on Corpus callosum (CC) and hippocampal regions CA1 on color-coded fractional anisotropy (FA) maps extracted from DTI. A monoexponential was fitted to the MGE data to compute T2* maps (qMRLab). Similar regions of interest (ROI) were again manually selected on Corpus callosum (CC) and hippocampal regions CA1.

Statistics: Mann-Whitney test ($p < 0.05$) was used on metrics extracted from DTI and DBSI and $T2^*$ between the control and the KI groups.

Submit to Organization for Human Brain Mapping (OHBM 2023), Montreal, CA. Please do not distribute until Mar. 21, 2023. (Version: Final)

Results

In the corpus callosum, 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* (Figure 1).

In CA1 of the hippocampus, we found evidence of major microstructural alterations 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. This was further confirmed by a significant increase in T2*. MGE allowed for higher resolution within an acceptable timeframe and provided striking alterations in KI animals as shown in Figure 2.

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 evaluation of disease progression and therapeutic response in future pediatric clinical trials.

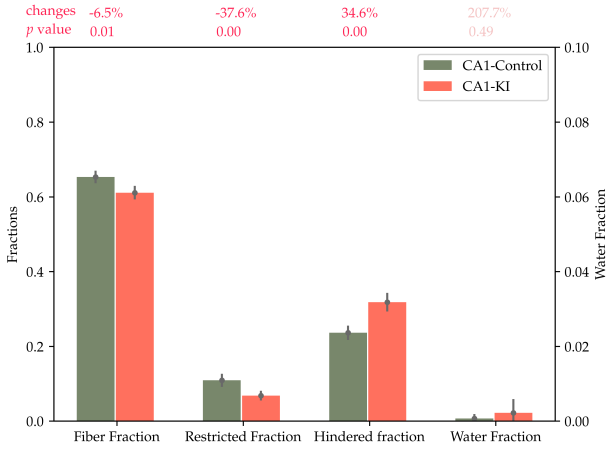
References

C Bartsocas, H Gröbe, J J van de Kamp, K von Figura, H Kresse, U Klein, and M A Giesberts. Sanfilippo type C disease: clinical findings in four patients with a new variant of mucopolysaccharidosis III. *Eur. J. Pediatr.*, 130(4): 251–258, April 1979.

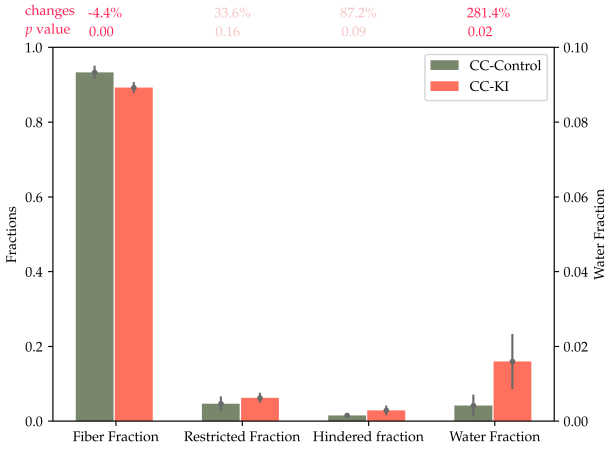
Carla Martins, Helena Hůlková, Larbi Dridi, Virginie Dormoy-Raclet, Lubov Grigoryeva, Yoo Choi, Alexander Langford-Smith, Fiona L Wilkinson, Kazuhiro Ohmi, Graziella DiCristo, Edith Hamel, Jerôme Ausseil, David Cheillan, Alain Moreau, Eva Svobodová, Zuzana Hájková, Markéta Tesařová, Hana Hansíková, Brian W Bigger, Martin Hrebícek, and Alexey V Pshezhetsky. Neuroinflammation, mitochondrial defects and neurodegeneration in mucopolysaccharidosis III type C mouse model. *Brain*, 138(Pt 2):336–355, February 2015.

Yong Wang, Qing Wang, Justin P Haldar, Fang-Cheng Yeh, Mingqiang Xie, Peng Sun, Tsang-Wei Tu, Kathryn Trinkaus, Robyn S Klein, Anne H Cross, and Sheng-Kwei Song. Quantification of increased cellularity during inflammatory demyelination. *Brain*, 134(Pt 12):3590–3601, December 2011.

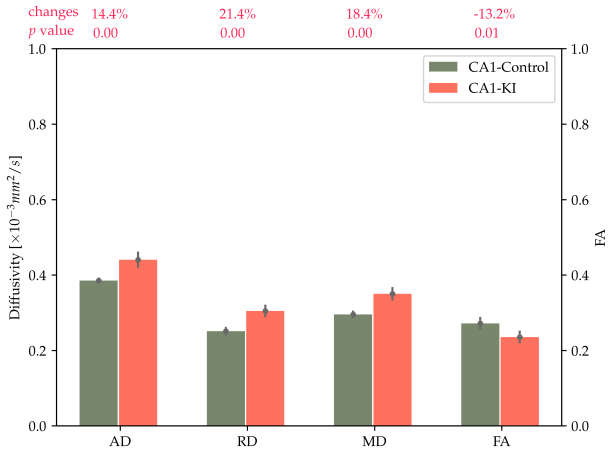
Figures



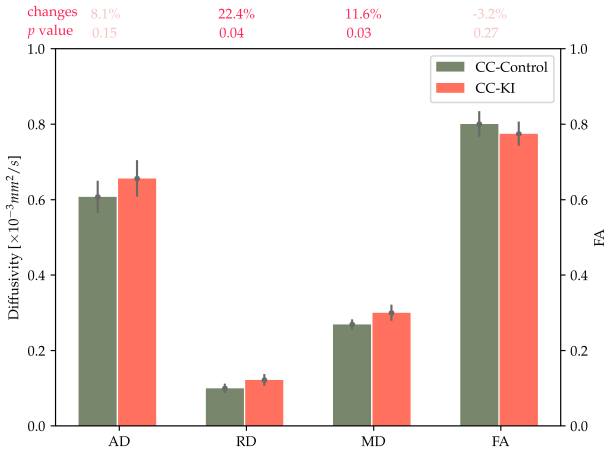
(a) DBSI results of CA1



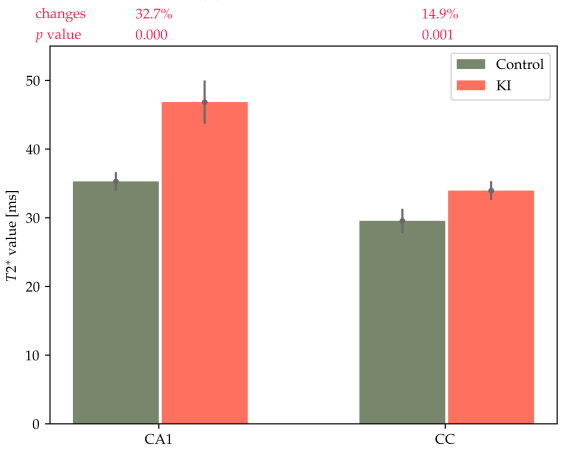
(b) DBSI results of CC



(c) DTI results of CA1

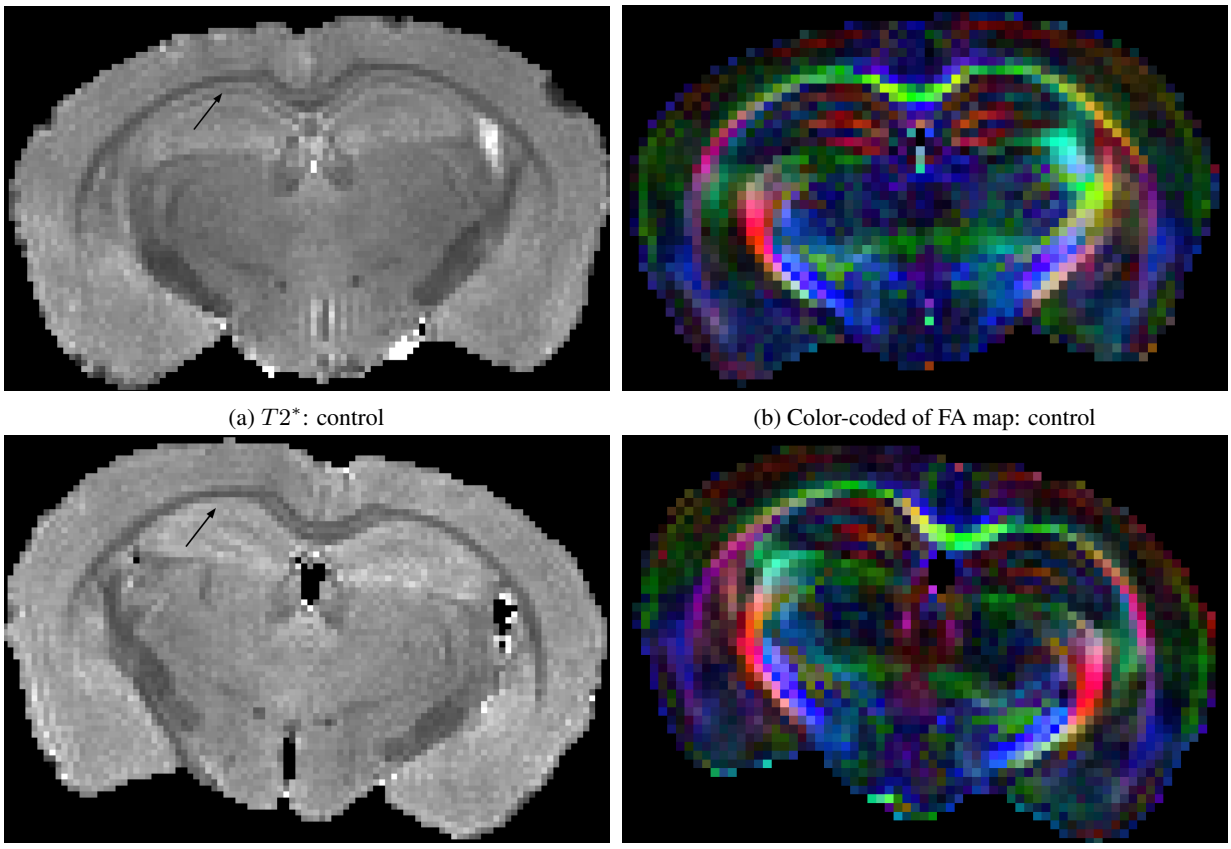


(d) DTI results of CC



(e) $T2^*$ results of CA1 and CC

Figure 1: Results from regions of interest placed in the corpus callosum and in the CA1 of the hippocampus on DBSI maps, DTI maps, and $T2^*$. Abbreviation: AD=axial diffusivity, RD = radial diffusivity, MD = mean diffusivity, FA = fractional anisotropy. For the p values and changes, values were aligned as KI vs Control on the top of each figure. Mann-Whitney test with test strength < 0.05 were used for statistics (red color for $p < 0.05$, pink color for $p \geq 0.05$).



(a) $T2^*$: control

(b) Color-coded of FA map: control

(c) $T2^*$: KI

(d) Color-coded of FA map: KI

Figure 2: Left column $T2^*$ map, Right column Fractional anisotropy map with color coded overlay. Note: changes in hippocampal microarchitecture (black arrow) on the $T2^*$ map.