



A ZOOM INTO CIBM MRI EPFL: NOVEL MULTIMODAL IMAGING APPROACHES TO STUDY THE BRAIN

Cristina Cudalbu, PhD
CIBM PCI EPFL

Master Course 2025-2026



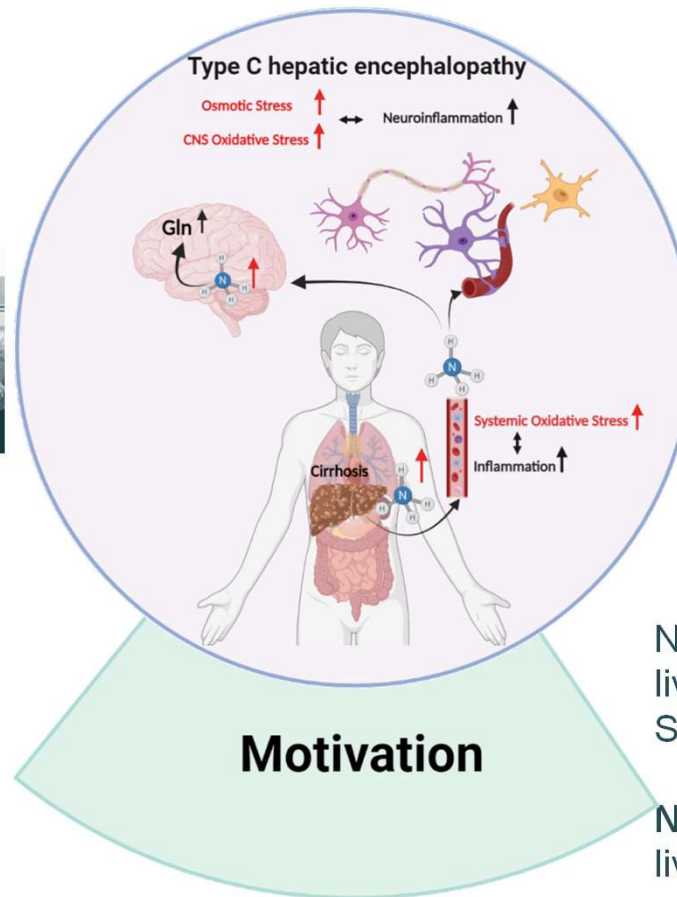
C I B M . C H

HEPATIC ENCEPHALOPATHY IN CHILDREN WITH CLD



- Daytime fatigue, irritable and aggressive behaviour
- Attention deficit
- Before and after liver transplantation in infants with biliary atresia
- Historically HE - reversible
- Unknowns:
 - impact of CLD on the neuro-cognitive and –psychiatric development
 - outcomes of children with CLD early in life
 - molecular, cellular and morphological underpinnings

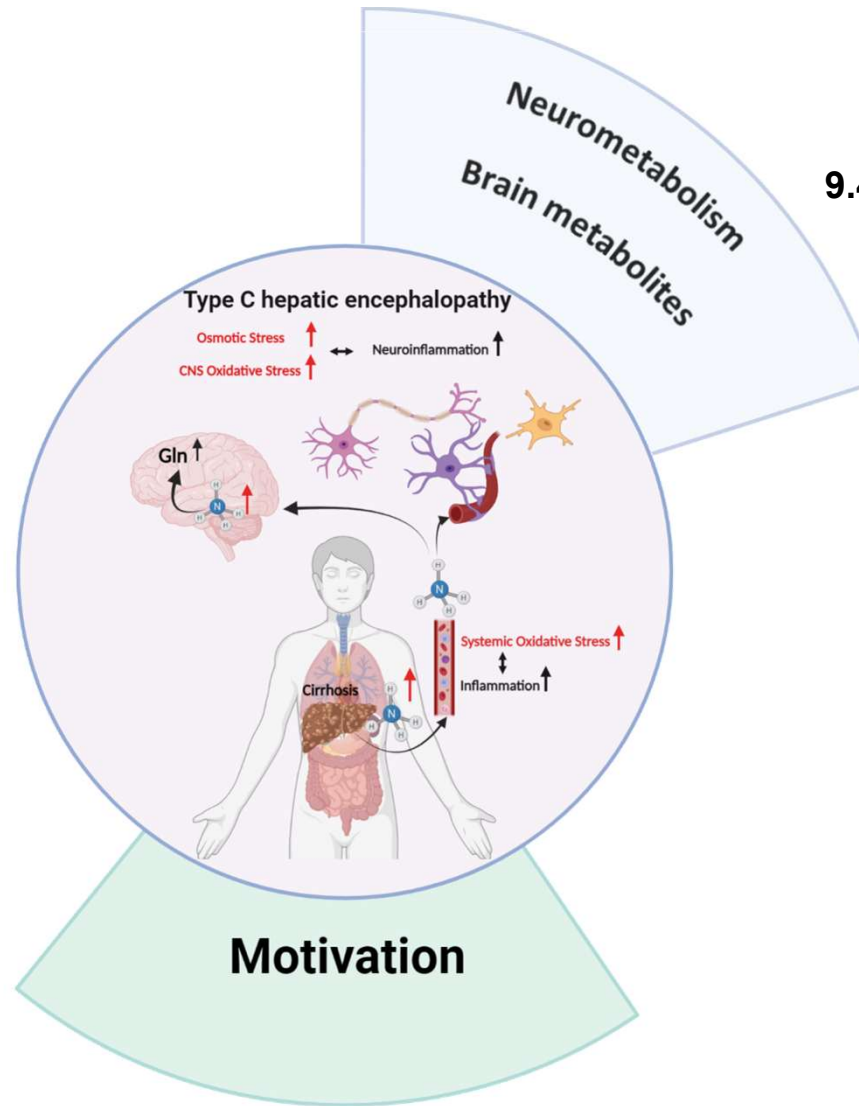
HEPATIC ENCEPHALOPATHY (HE)



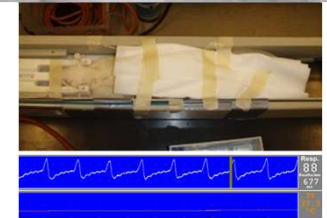
Neuropsychiatric syndrome → acute or chronic liver disease (125mil)
Severe loss of quality of life

Neurocognitive problems persist in kids after liver transplantation

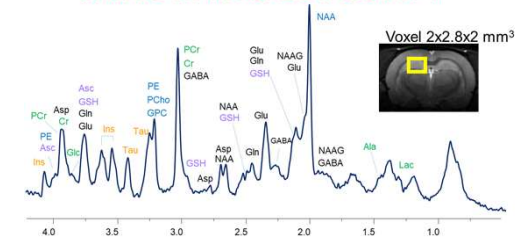
HE + METABOLISM



9.4T MRI system  Center for Biomedical Imaging



IN VIVO 1H MR SPECTROSCOPY



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MODEL



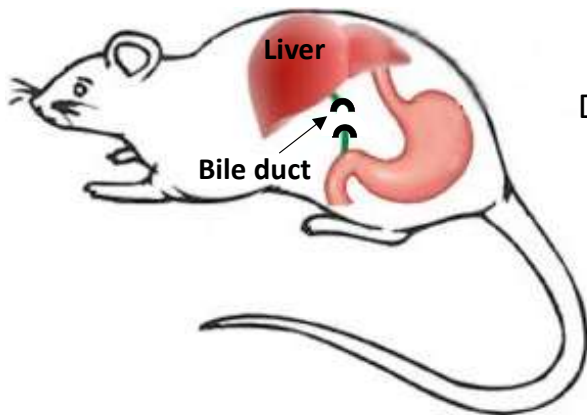
Longitudinal neurometabolic changes in the hippocampus of a rat model of chronic hepatic encephalopathy

Olivier Braissant^{1,†}, Veronika Rackayova^{2,3,†}, Katarzyna Pierzchala³, Jocelyn Grosse⁴, Valérie A. McClain⁵, Cristina Cudalbu^{1,2}

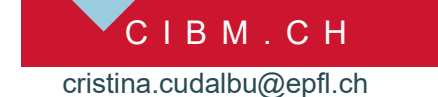
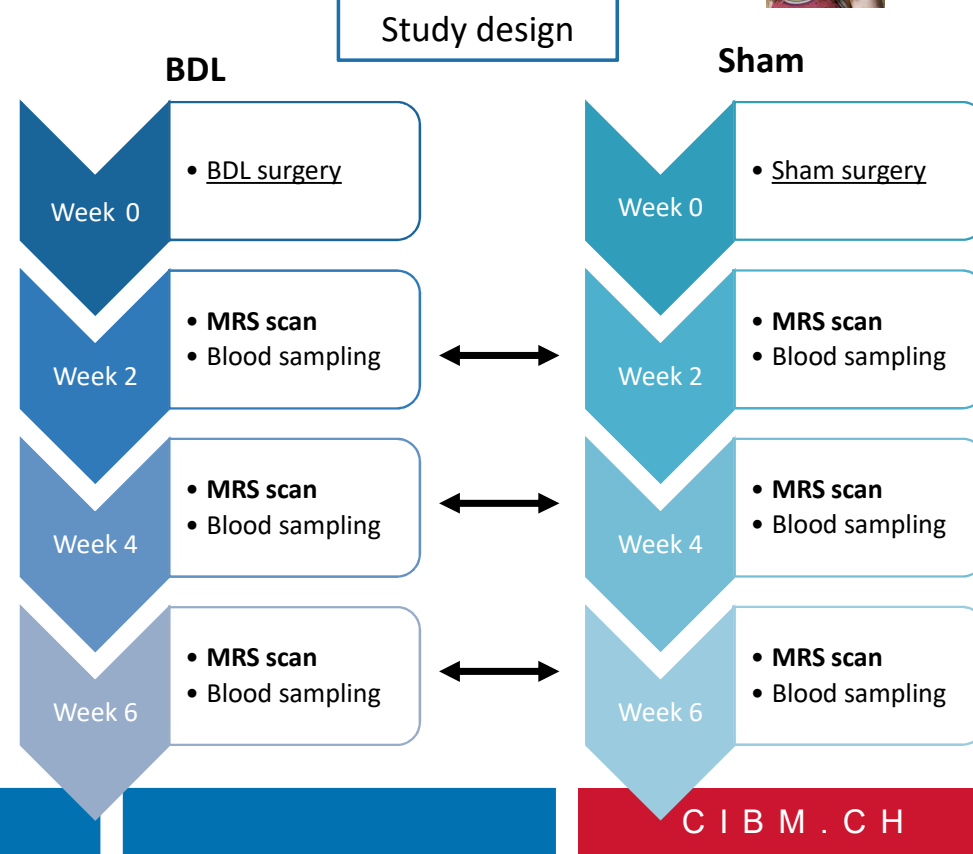
Animal model of chronic liver disease (CLD)

Developing brain → Adult rats & Pup rats 21 days old (P21) – corresponding to 9 months old human baby¹

Bile Duct Ligated (BDL) rats (Wistar)
→ recognized by ISHEN² – type C HE



Surgical ligation of the bile duct
↓
Development of chronic liver disease
↓
Neurological disease
Hepatic Encephalopathy



^[1]Workman et al. 2013; ^[2]DeMorrow et al, 2021

IN VIVO ¹H MR SPECTROSCOPY @ 9.4T

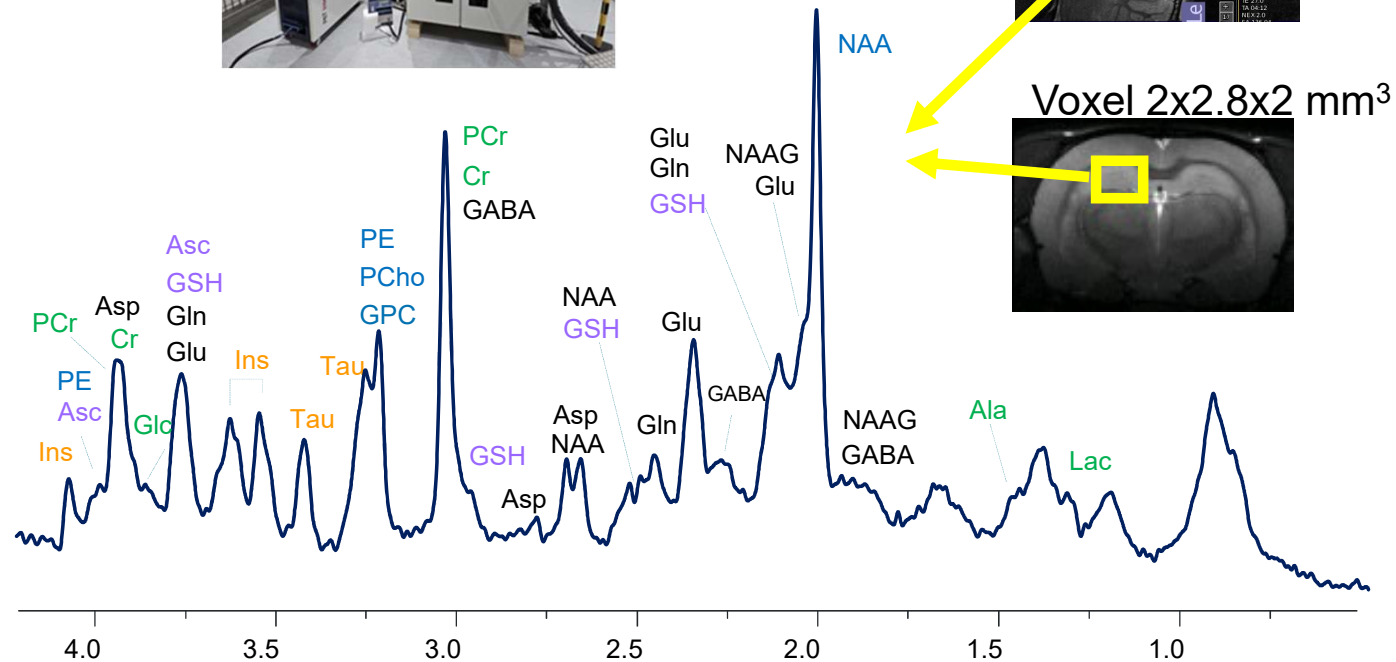
- *in vivo*
- non invasive



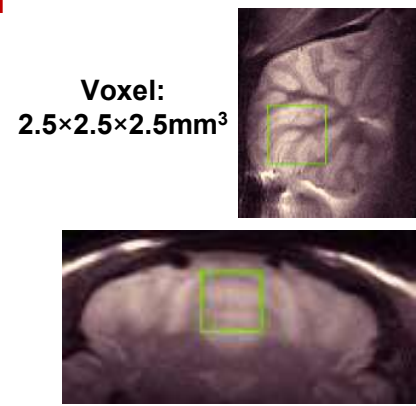
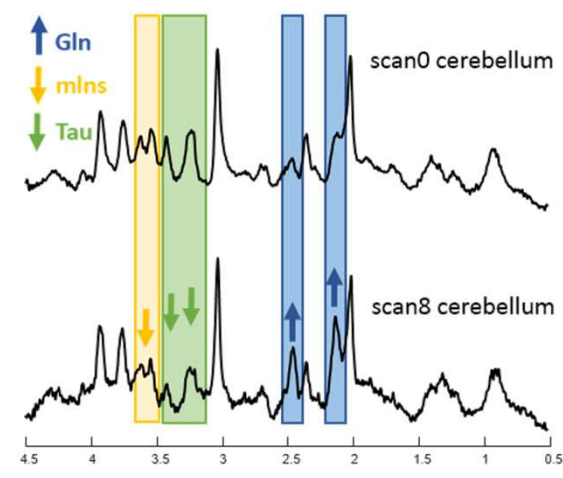
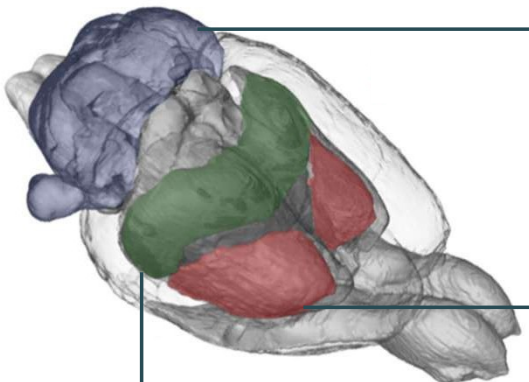
Neurochemical Profile

>18 Markers of :

- Myelination/Cell proliferation
- Energy metabolism
- Osmoregulation
- Neurotransmitter metabolism
- Antioxidants

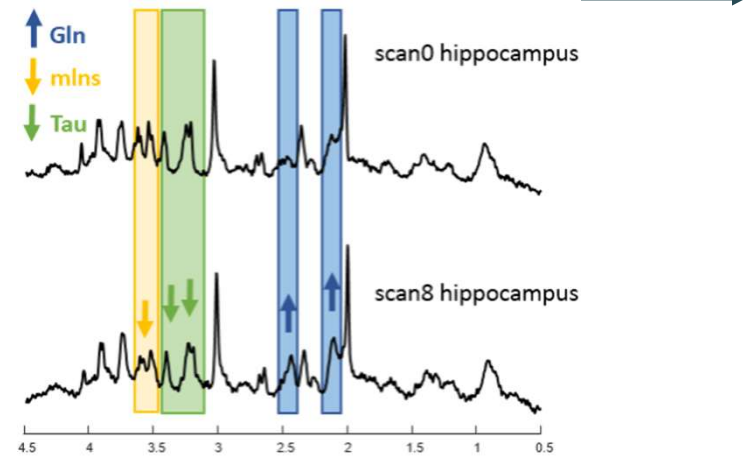
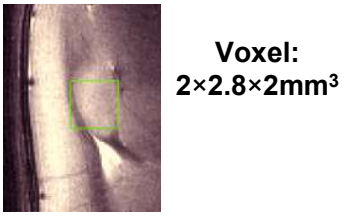
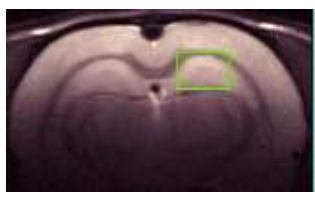


Cerebellum **+++ Gln**

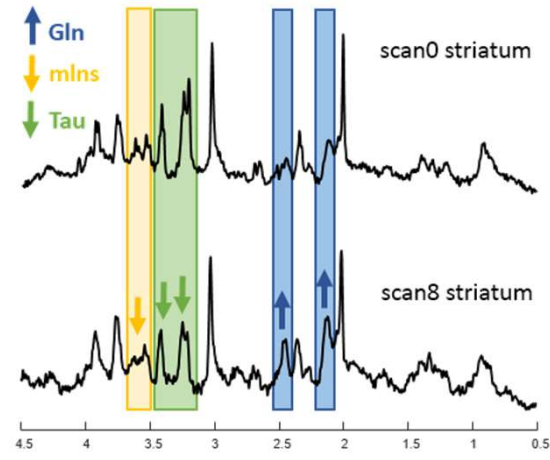
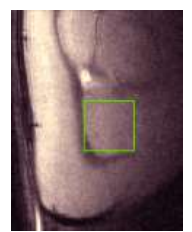
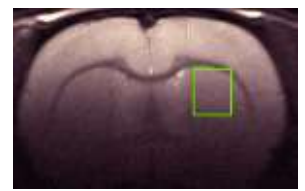


Spatial navigation
Learning (procedural and motor)
Working memory

Hippocampus



Striatum



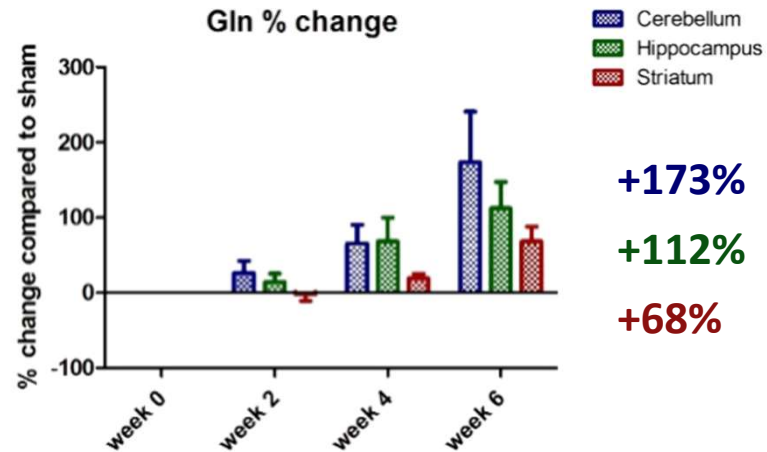
Control of motor movement
Decision making (motivation and emotions)

Spatial memory and spatial information encoding
Pattern separation and context related functions

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cristina.cudalbu@epfl.ch

DEVELOPING BRAIN DURING TYPE C HE



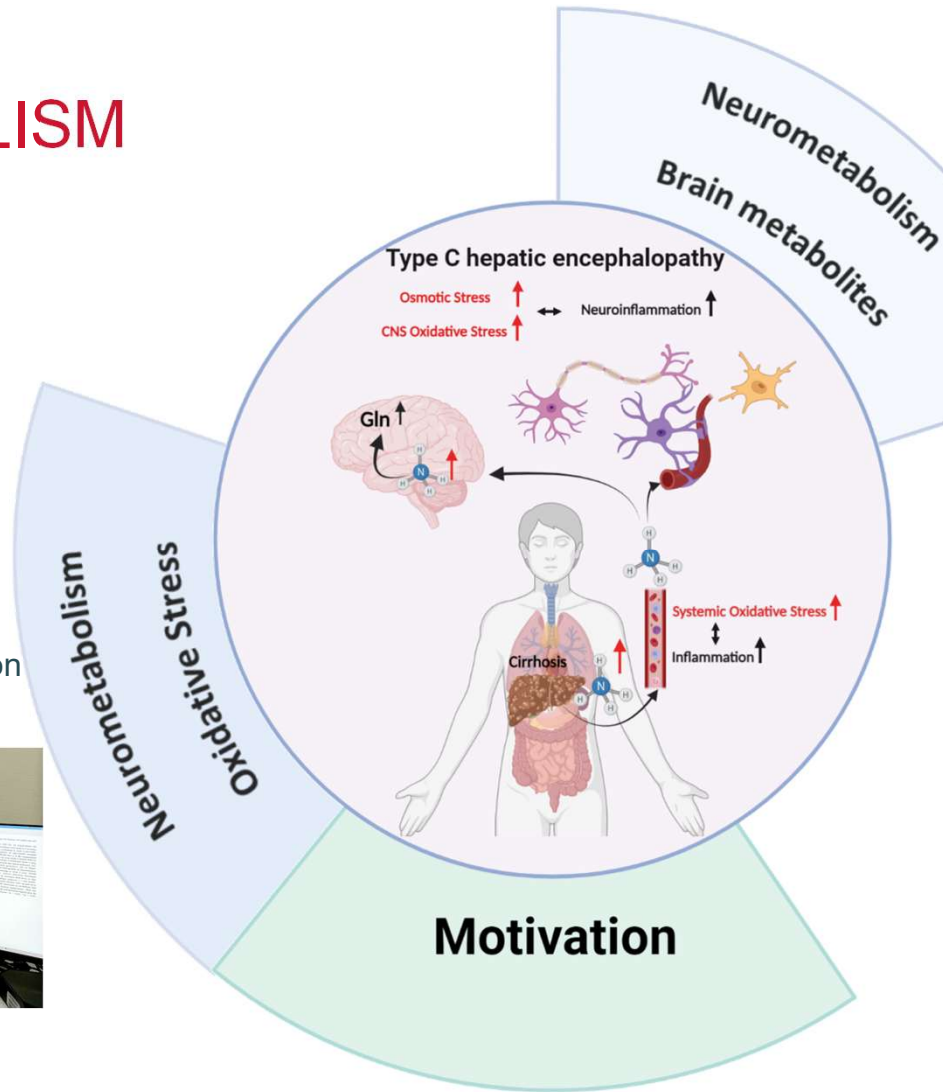
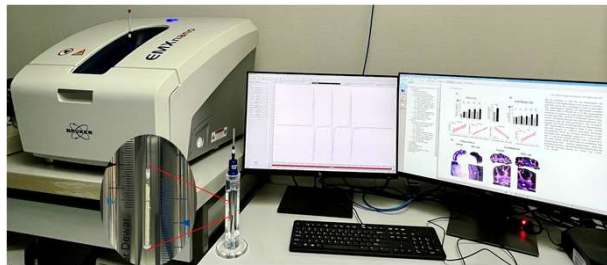
❖ Gln increase is the strongest in cerebellum

- Brain metabolites – several functions/roles in the brain
- **Antioxidant changes:** ↓ Asc, ↑ GSH in cerebellum
- **Energy metabolism:**
 - ↑ Lac and ↓ PCr, Cr
 - Cr, PCr – several roles in the brain

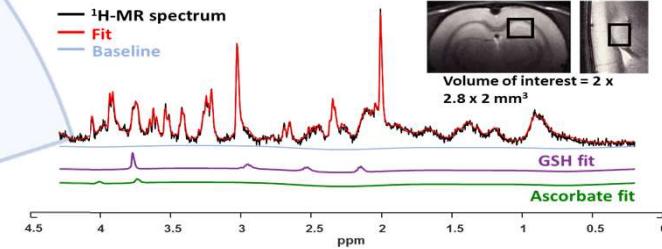
Need of multimodal complementary approaches

HE + METABOLISM

EPR spectroscopy – direct detection of reactive oxygen species



Hippocampus



Antioxidants

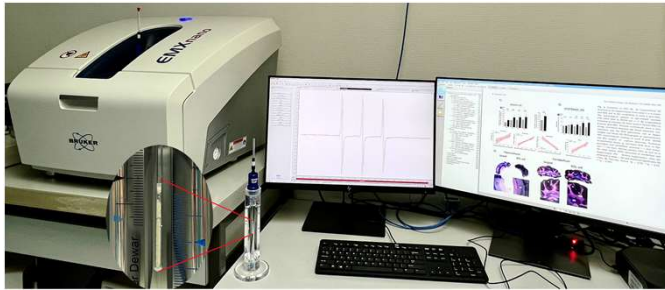
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katarzyna.pierzchala@epfl.ch

OXIDATIVE STRESS DETECTION

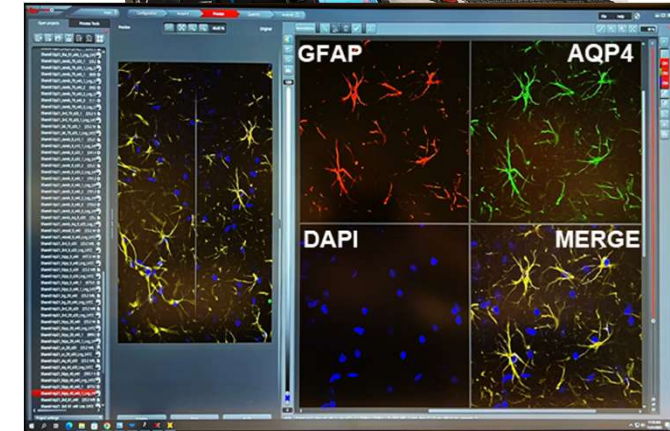
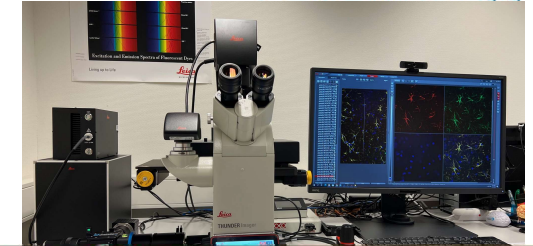
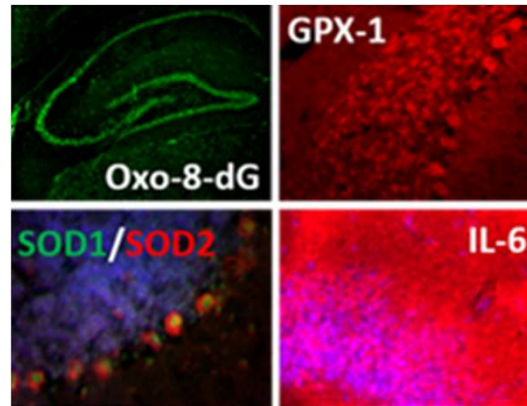


EPR – ex-vivo direct detection of oxidative stress with spin probe - CMH

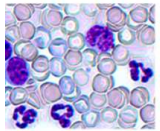


Tissue (i.e., brain, ...), cells lines / 3D organoids, and body fluids (CSF, blood, plasma, etc.)

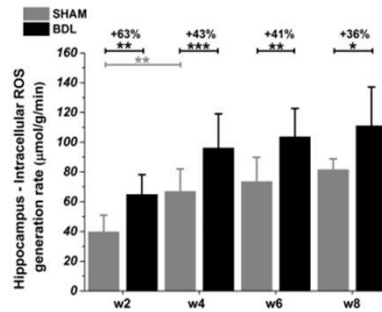
Immunohistochemistry – ex-vivo detection of oxidative stress with specific antibodies



Blood 7 μ L



BRAIN OS



Brain

50 μ L



Central nervous system and systemic oxidative stress interplay with inflammation in a bile duct ligation rat model of type C hepatic encephalopathy

K. Pierzchala^{a,b,c,d}, D. Simicic^{a,b,c,d}, A. Sienkiewicz^{a,c}, D. Sessa^f, S. Mitrea^{a,b}, O. Braissant^g, V. A. McLin^h, R. Gruetter^{a,c}, C. Cudalbu^{a,b}



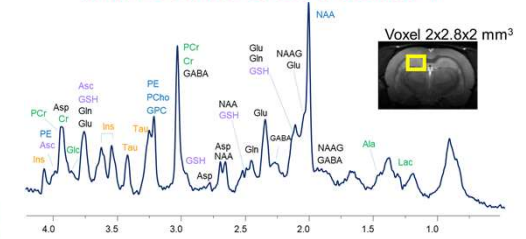
D.Simicic, et al, Anal Biochem. 2022; Pierzchala, K., et al., Free Radic Biol Med, 2022;

katarzyna.pierzchala@epfl.ch

HE + METABOLISM

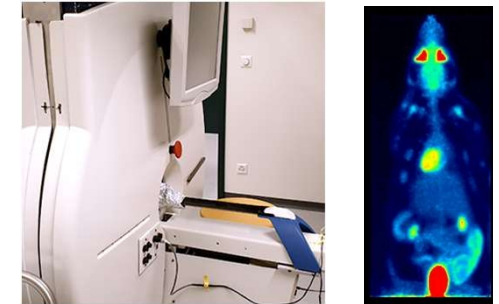


IN VIVO 1H MR SPECTROSCOPY



Energy metabolism ???

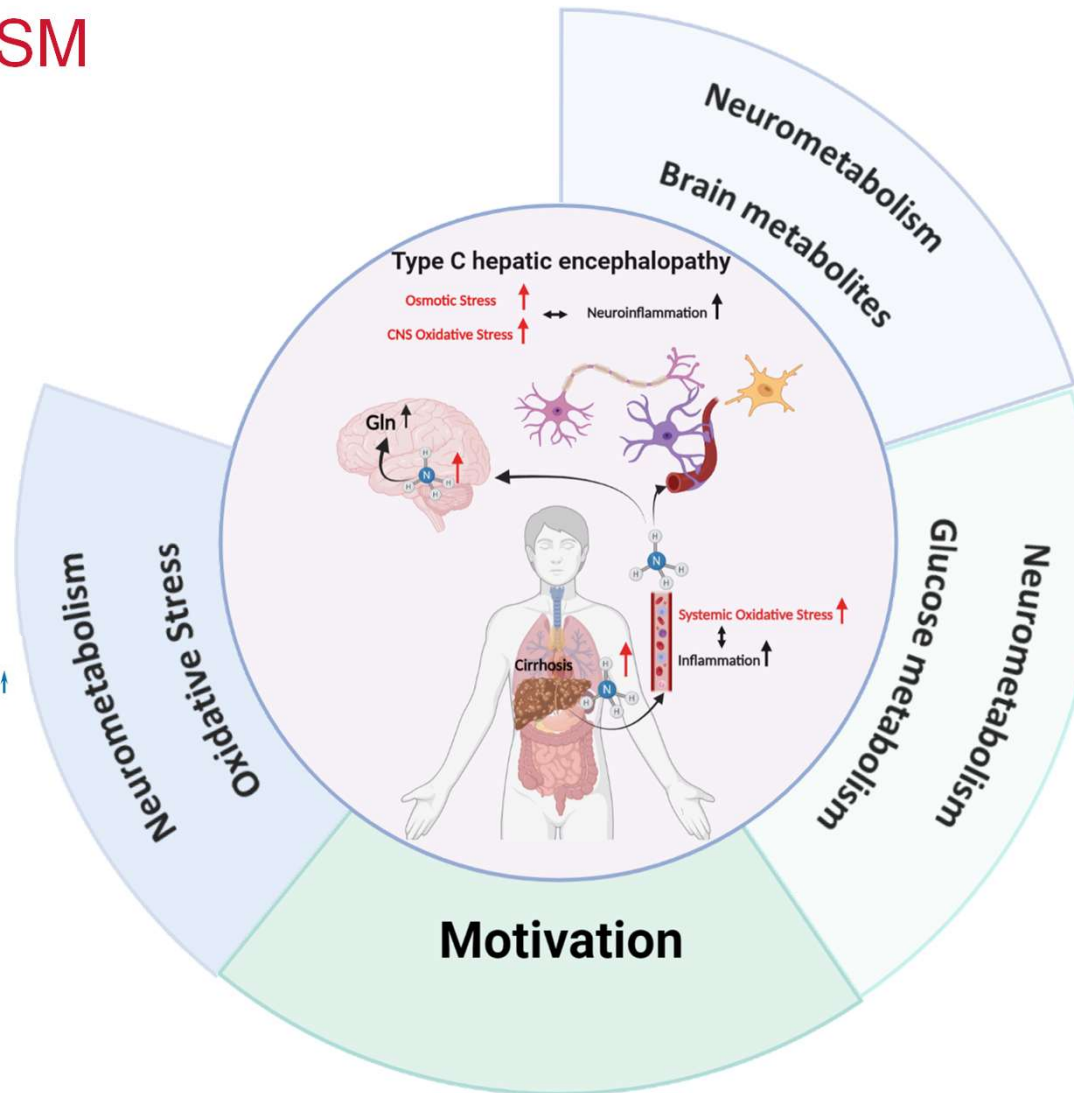
Gamma Medica-Ideas, Inc.



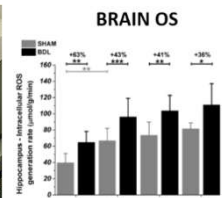
¹⁸F-FDG PET

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bernard.lanz@epfl.ch

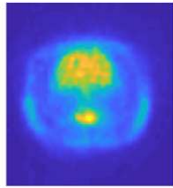


EPR spectroscopy – direct detection of reactive oxygen species

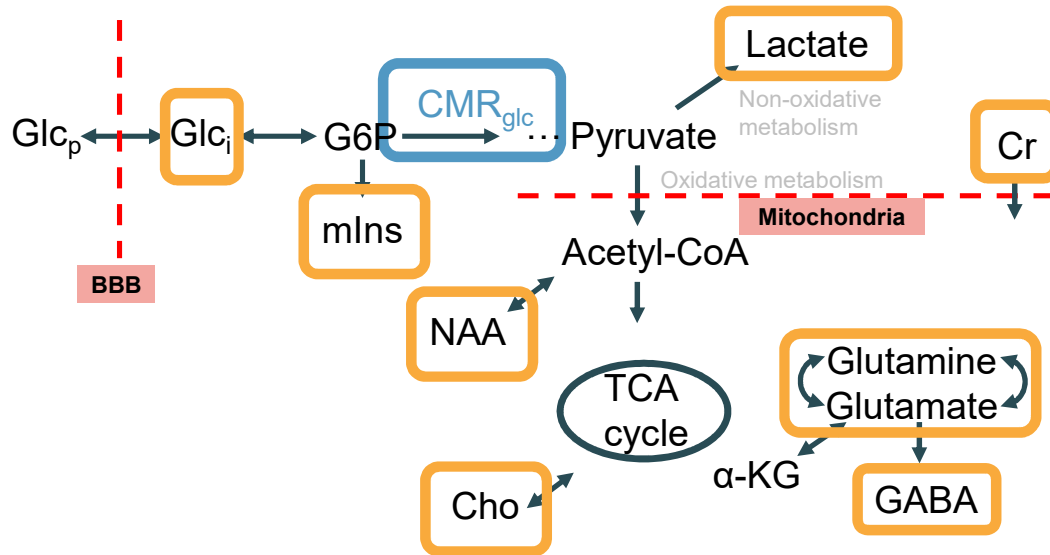


ENERGY METABOLISM

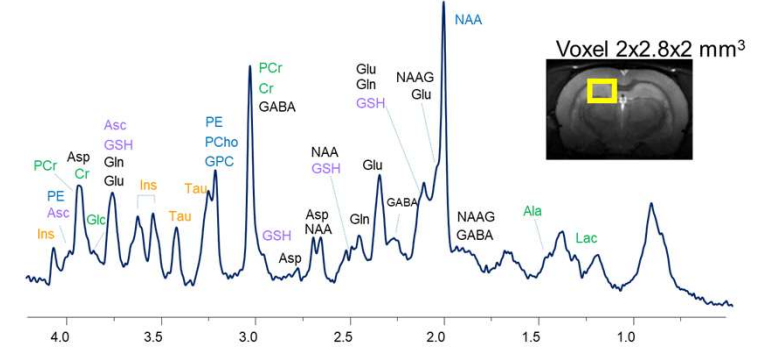
¹⁸F-FDG PET



Dynamic information on the total glucose uptake (cerebral metabolic rate of glucose [CMR_{glc}])

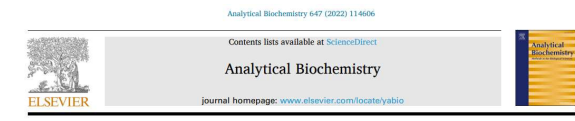
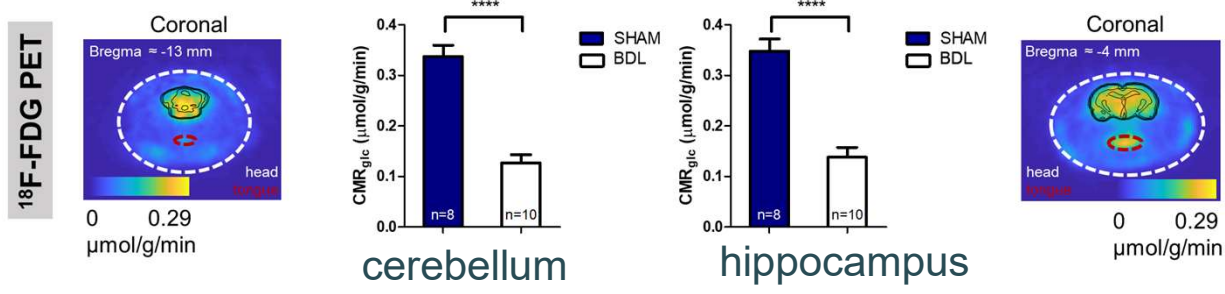


IN VIVO 1H MR SPECTROSCOPY



Static information on metabolite pools
Metabolites involved in a variety of brain functions

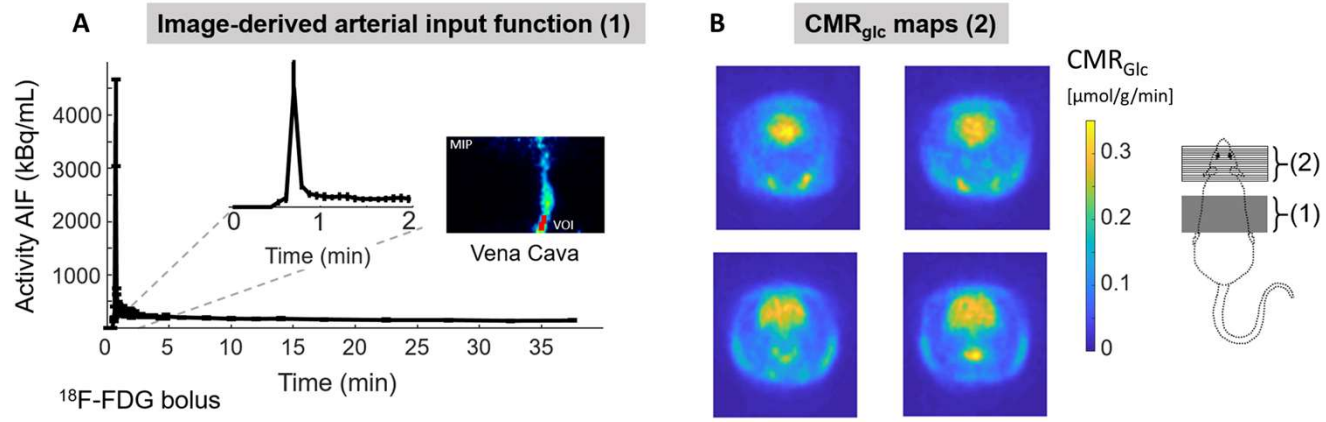
GLUCOSE CEREBRAL METABOLIC RATE WITH FDG PET



PET CMR_{glc} mapping and $^1\text{H-MRS}$ show altered glucose uptake and neurometabolic profiles in BDL rats

Jessie Mosso^{a,b,c}, Ting Yin^{a,b}, Carole Poitry-Yamate^a, Dunja Simicic^{a,b,c}, Mario Lepore^{a,b}, Valérie A. McLin^a, Olivier Braissant^a, Cristina Cudalbu^{a,b}, Bernard Lanz^{a,b,c,d}

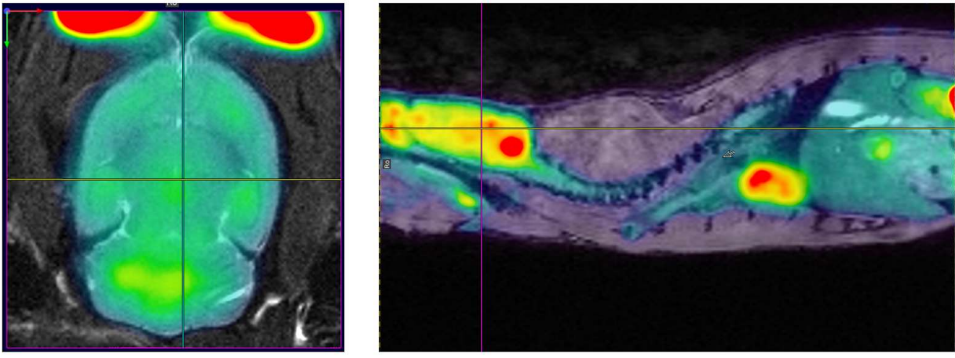
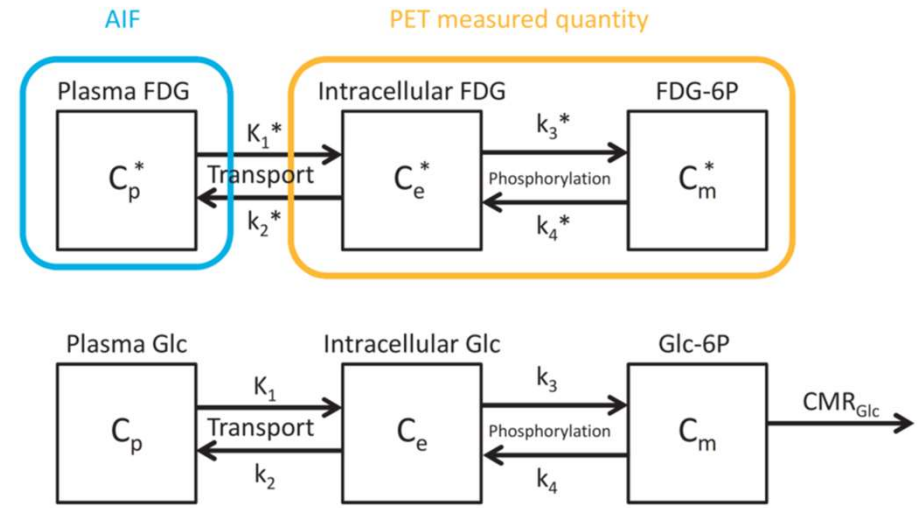
Two-fold lower CMR_{glc} in **HE** rats compared to control



Metabolic imaging - quantitative approach with minimal invasiveness

Method for non-invasive quantification of CMR_{glc} in rodent brain

UNIQUE 9.4T MR/PET SYSTEM @CIBM PCI EPFL

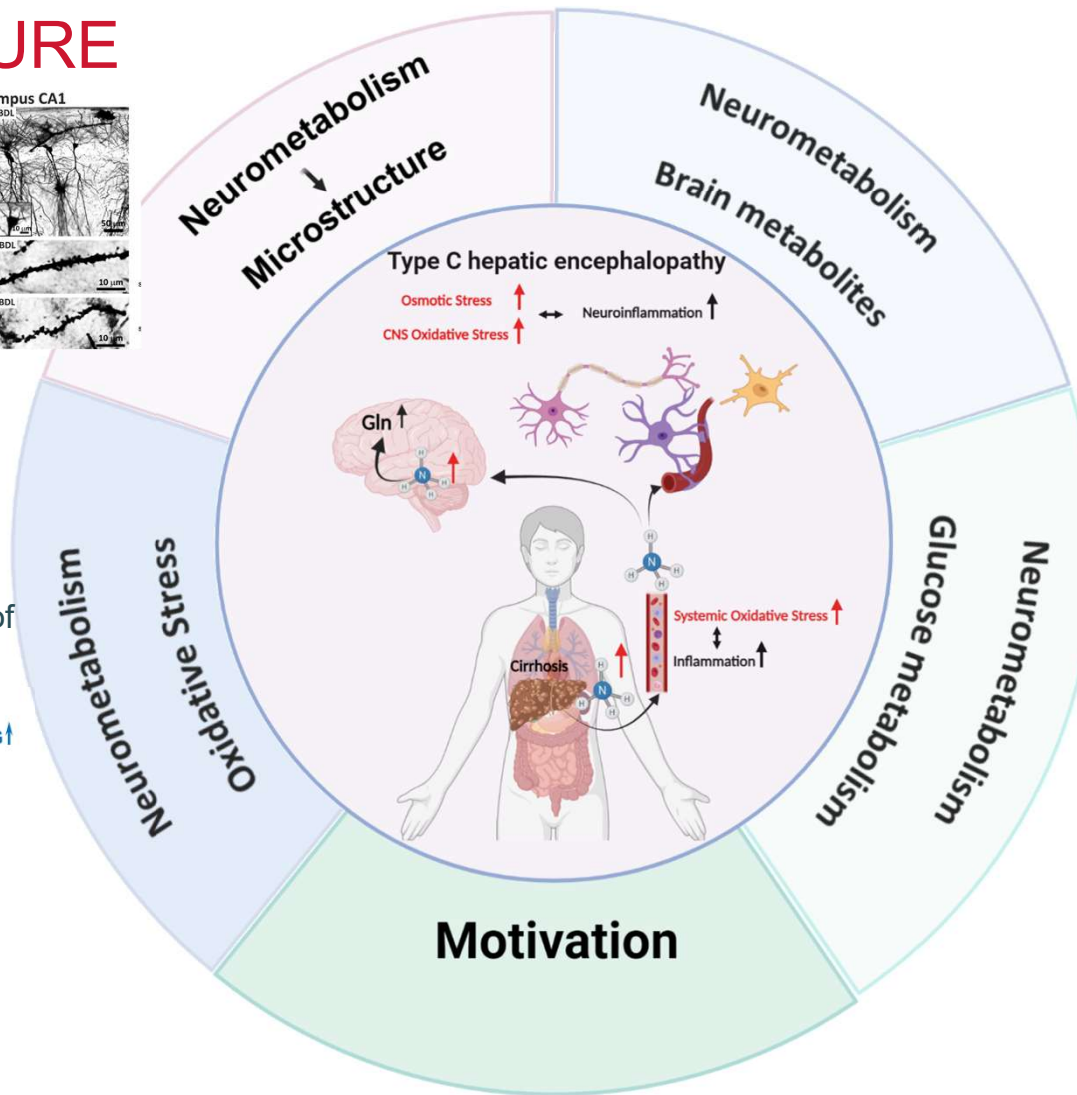
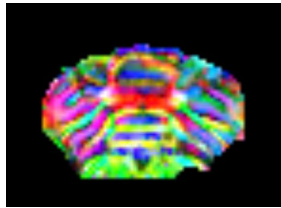
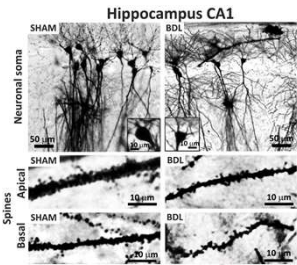
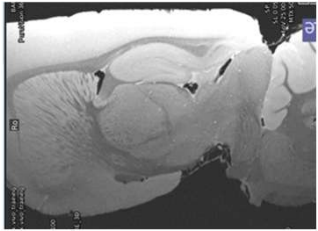


First **dynamic MR-PET** examinations in the rat brain and body using ^{18}F - FDG

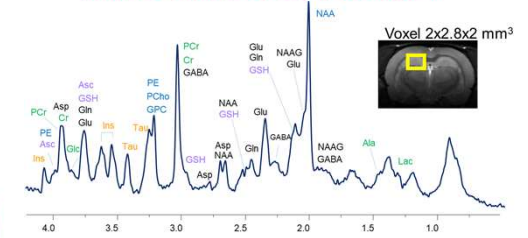
Metabolic model used to generate 3D metabolic maps of the cerebral metabolic rate of glucose (CMR_{glc}).

Quantitative dynamic FDG-PET probes metabolic reaction rates *in vivo* with high sensitivity.

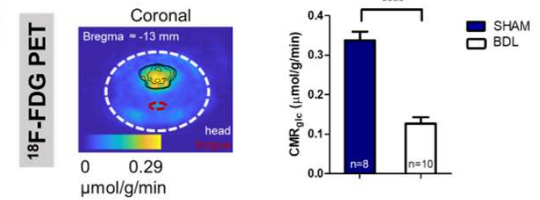
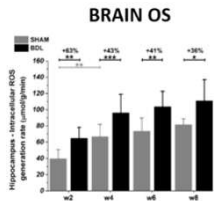
MICROSTRUCTURE



IN VIVO 1H MR SPECTROSCOPY



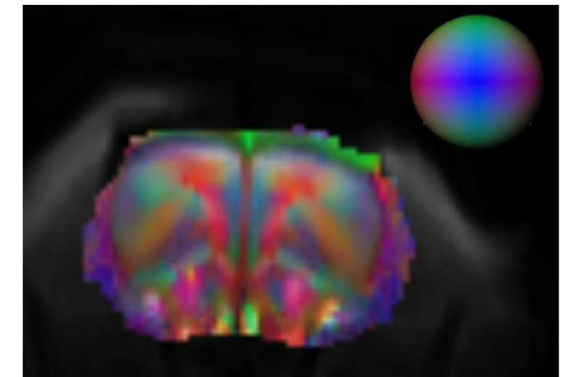
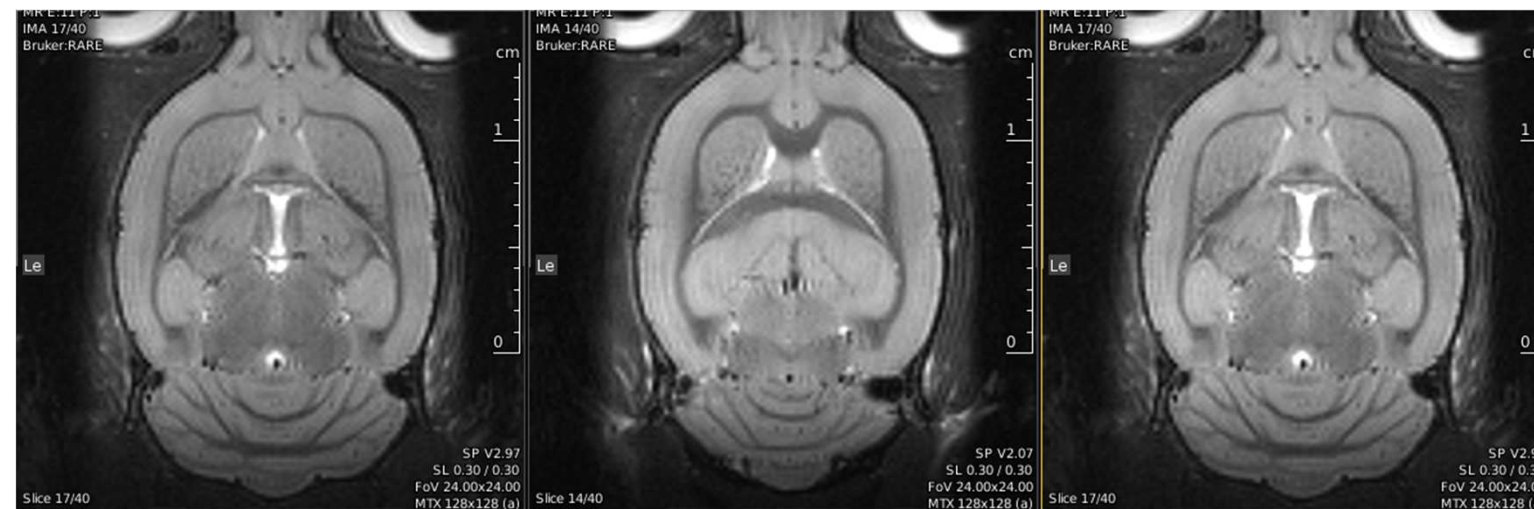
EPR spectroscopy – direct detection of reactive oxygen species

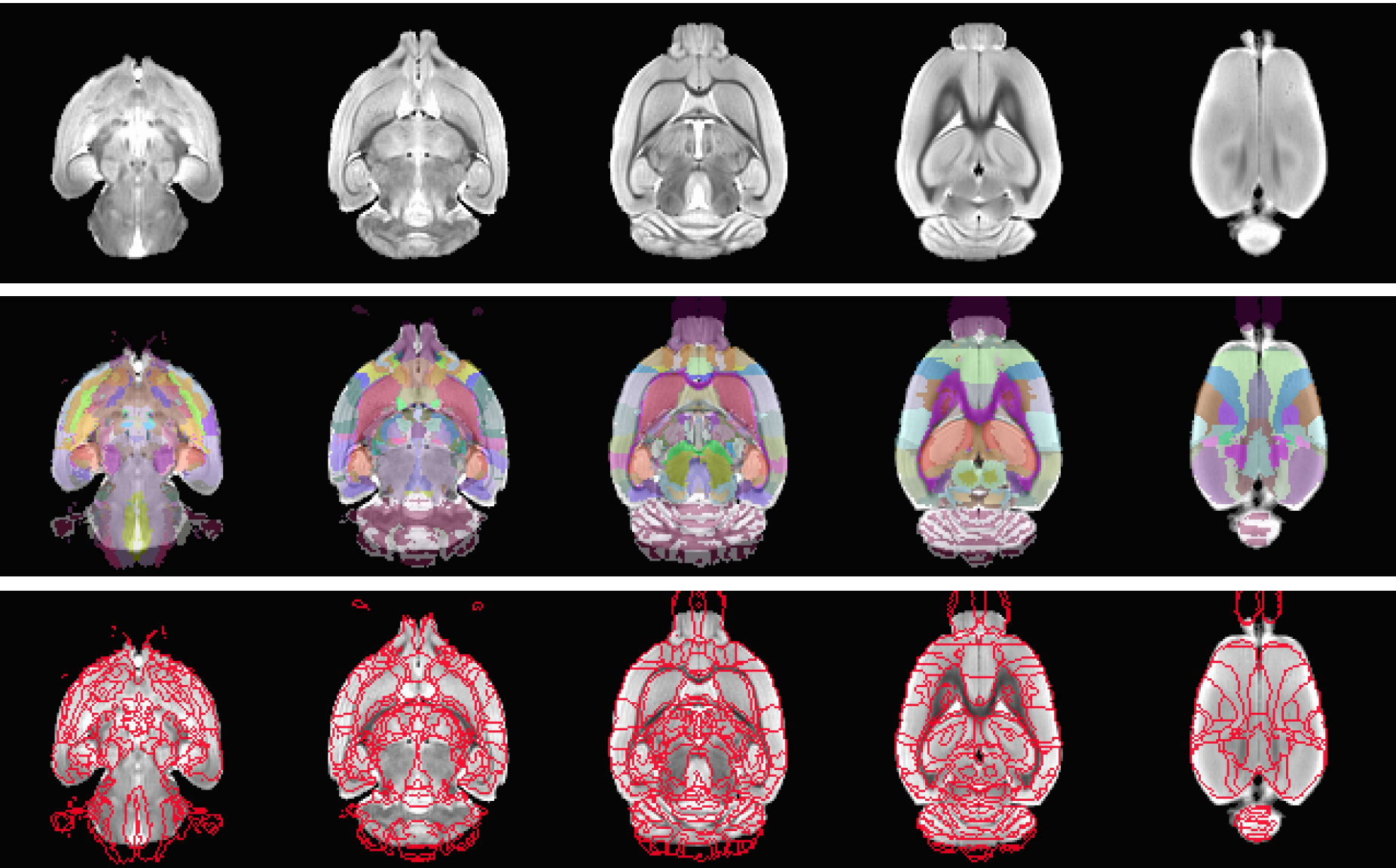




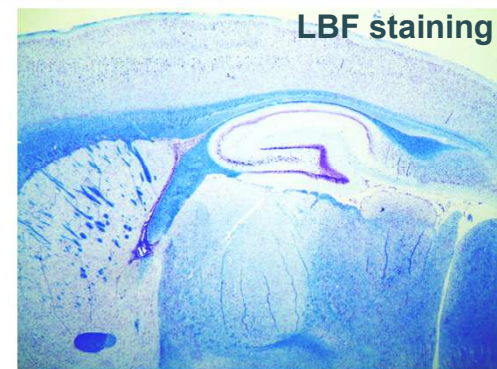
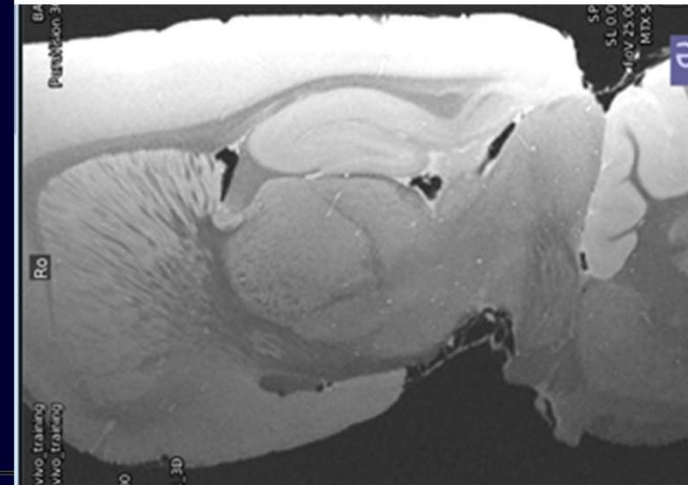
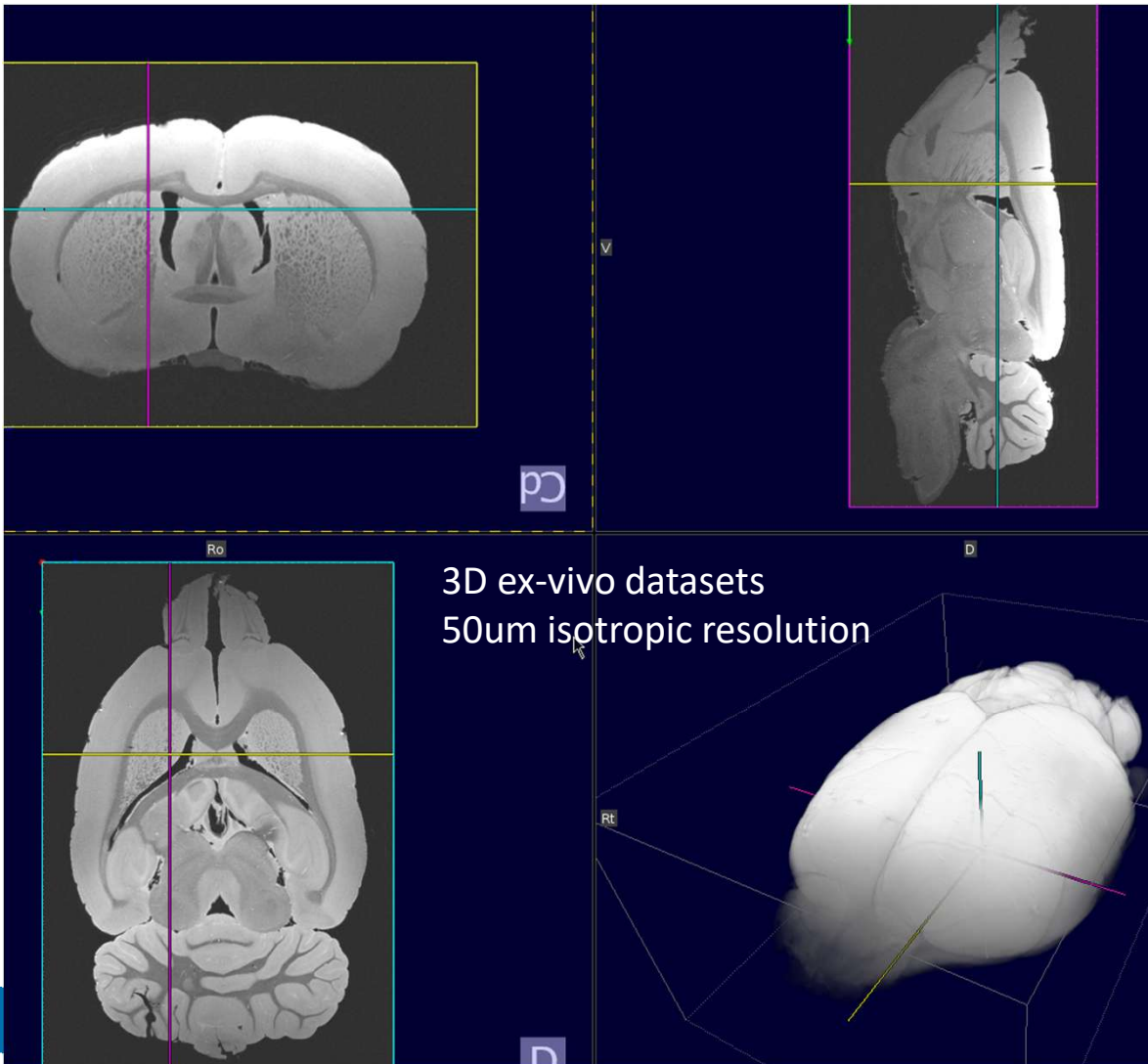
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3min acq/orientation

0.18x0.18x0.3mm³
15min acq



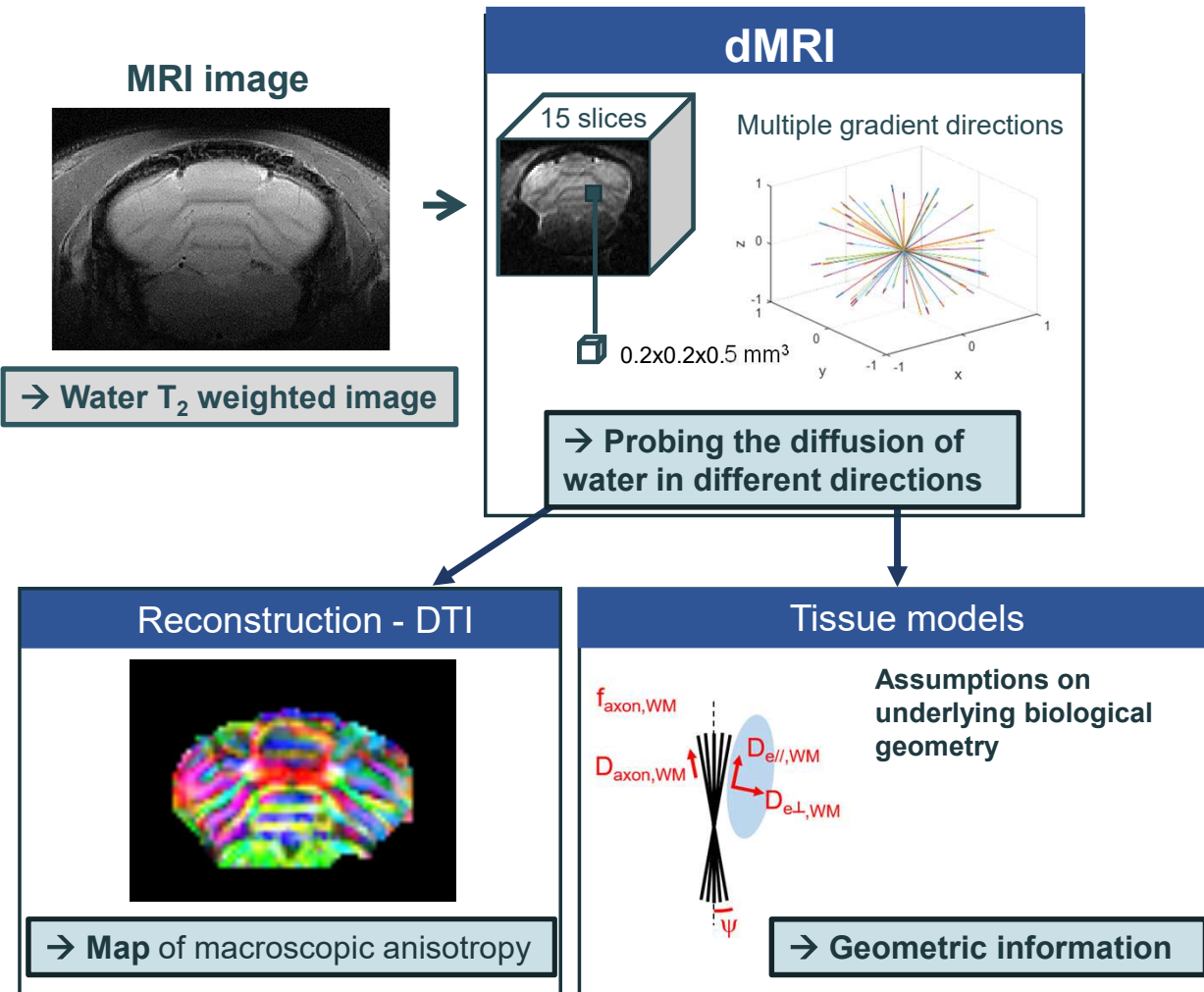


APPROACHING THE MICROSCOPY RESOLUTION

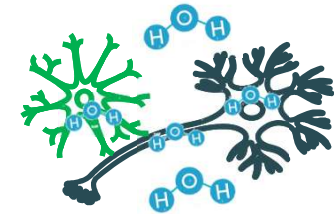
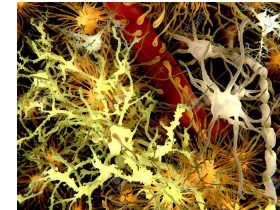


Histology-MRI registration
and extraction of
quantitative histology
metrics

Diffusion Weighted MRI (dMRI)



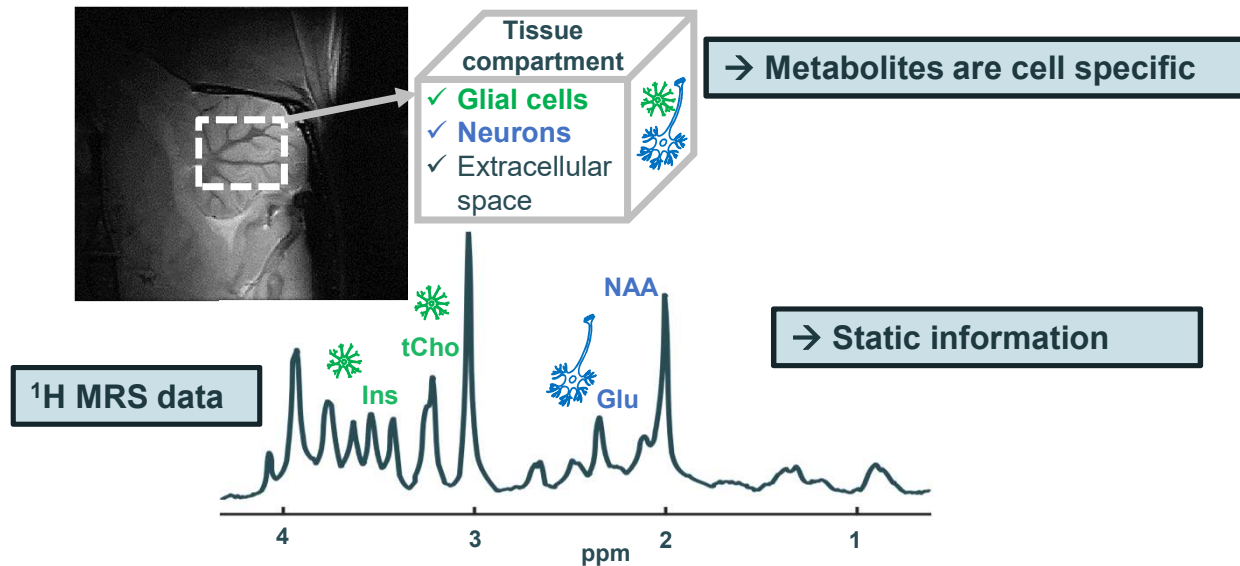
1 Water is not compartment specific



Water is everywhere!!!

Magnetic resonance spectroscopy (MRS)

1 Metabolites are compartment specific



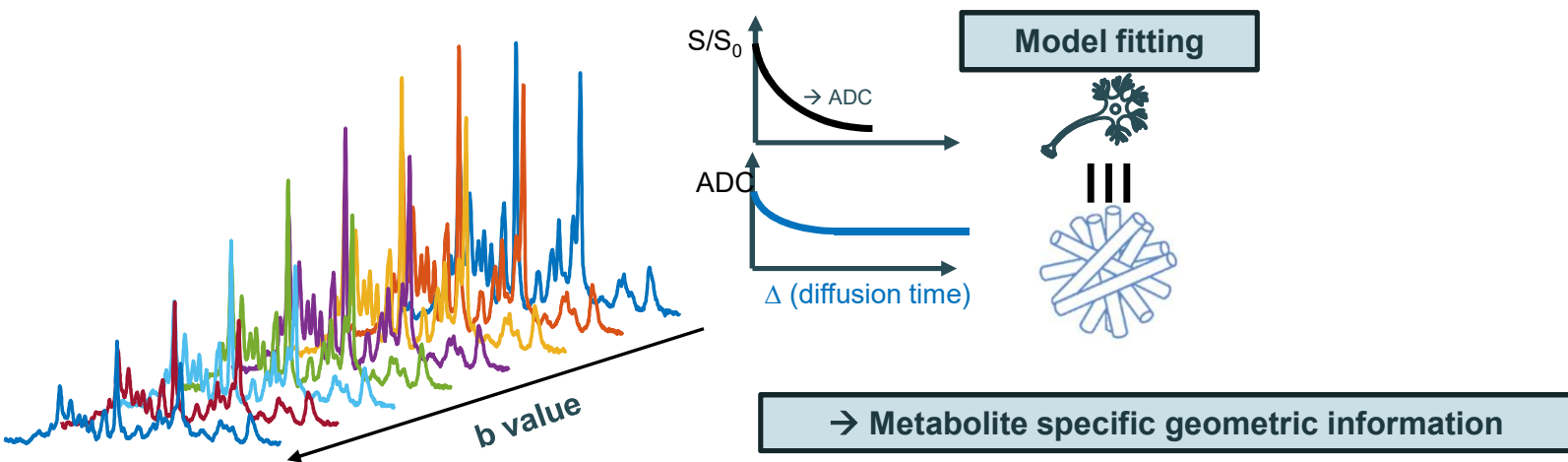
[Ins] ~ 3x higher in astrocytes compared to neurons¹

[tCho] ~ 6x higher in glia compared to neurons^{2,3}

[NAA] & [Glu], large consensus mostly in neurons

(1) Fisher S et al., J Neurochem 2002; (2) Urenjak J et al., J Neurosci. 1993; (3) Le Belle JE et al. NMR Biomed. 2002

Diffusion Weighted MRS (dMRS)



! Metabolite = cell-specific information



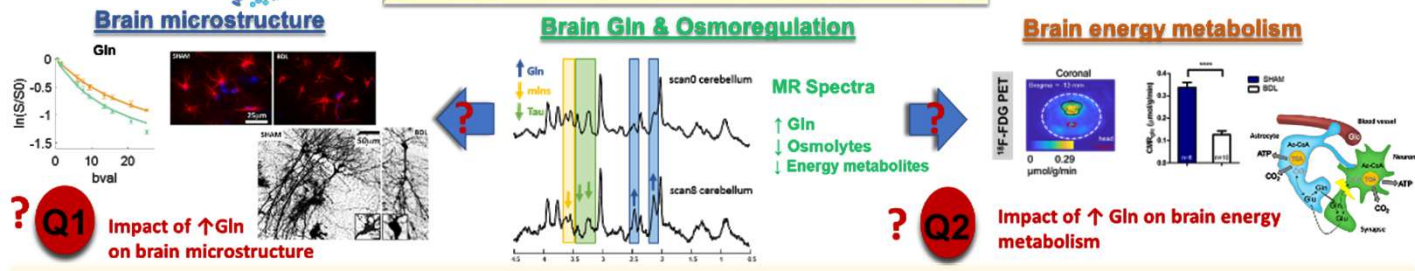
J Mosso



- ✓ Cellular morphology
- ✓ Cytosol viscosity
- ✓ Tortuosity
- ✓ Exchange
- ✓ Compartmentation
- ✓

Palombo et al. *Neuroimage* 2017; Mosso et al, *MRM* 2024 & *Front Neurosci.* 2024; Mougél et al *MRM* 2022 & *J Magn Reson* 2022

Chronic HE: Previous work and unknowns

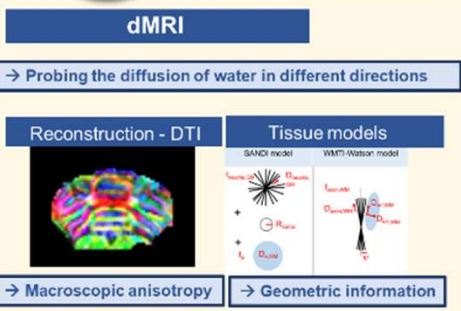


Q1 Impact of ↑Gln on brain microstructure

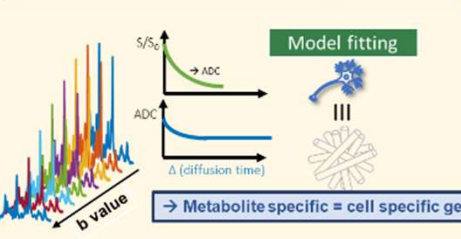
Q2 Impact of ↑Gln on brain energy metabolism

Current proposal : in animal models, organoids and children with type B and C HE

W1&3 Assess the effects of ↑Gln on brain microstructure using:

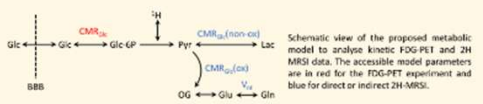
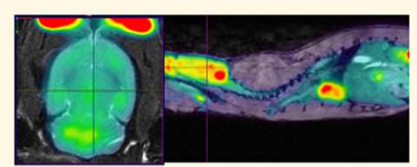


Diffusion Weighted MRS (dMRS)

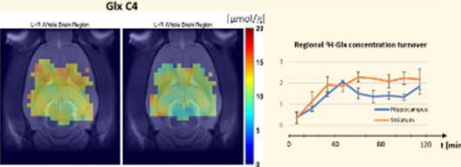


W2&3 Assess the effects of ↑Gln on brain energy metabolism using:

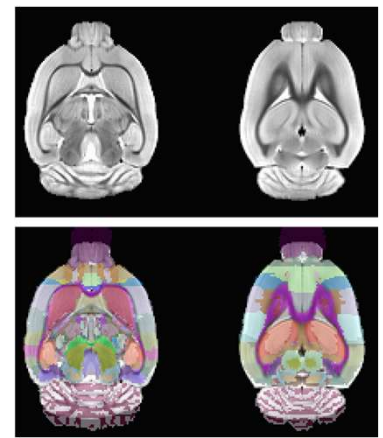
Dynamic PET-MR: Glc uptake



Dynamic 2H-MRSI: Glc metabolism

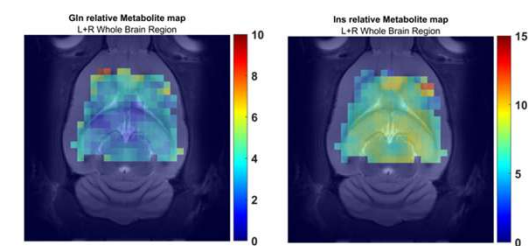


High resolution MRI: volumetry

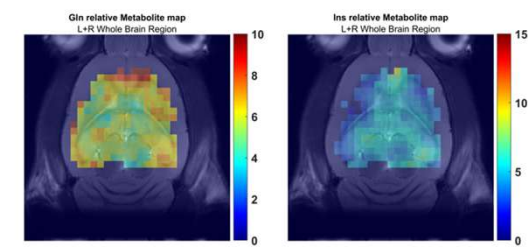


Courtesy of Tan Toi Phan

Sham



BDL

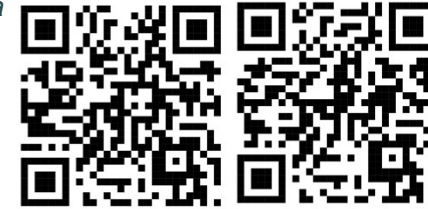


Courtesy of D Simicic and J Mosso

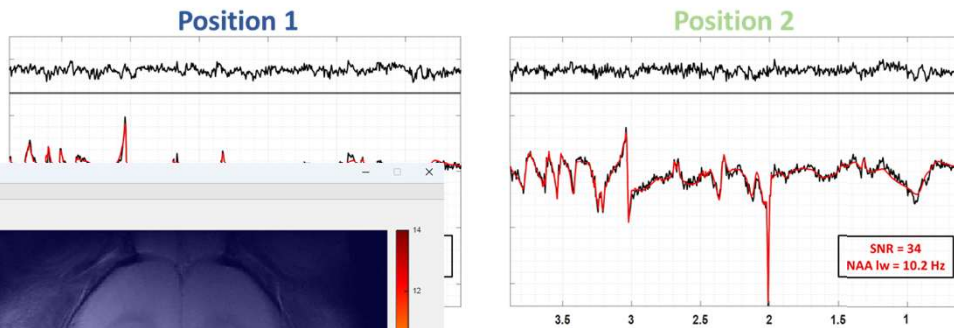
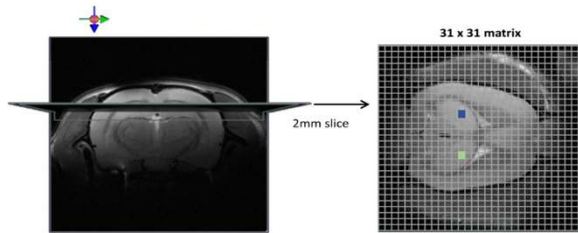
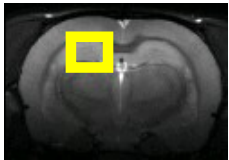
Courtesy of B Lanz and A Siviglia

Courtesy of Gianna Nossa

METABOLIC MAPPING via MRSI



Voxel $2 \times 2.8 \times 2 \text{ mm}^3$



FID- MRSI
 $0.7 \times 0.7 \times 2 \text{ mm}^3$
13 min @14.1T

<https://www.epfl.ch/labs/mrs4brain/ressources/mrs4brain-toolbox/>

MRS4Brain Toolbox

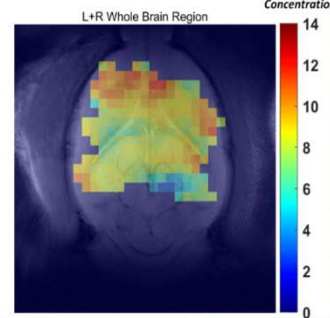
Data management: Bruker data folder, Result folder, Study name

Processing steps: Number slices, PDF document, Lipid suppression, Filigaps, Denoising, Reconstruction

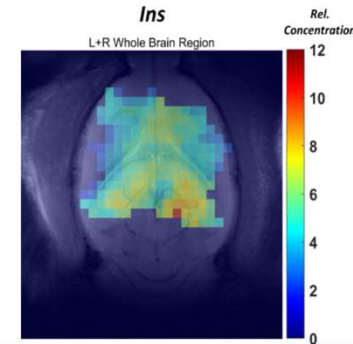
Data specific: Experiment number folder, Metabolites, MRI Slice

Relative metabolite map: Glu, Ins, tCho

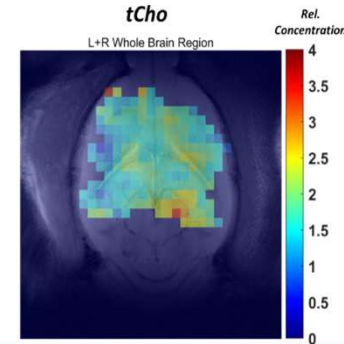
Relative metabolite map: **Glu**



Relative metabolite map: **Ins**



Relative metabolite map: **tCho**

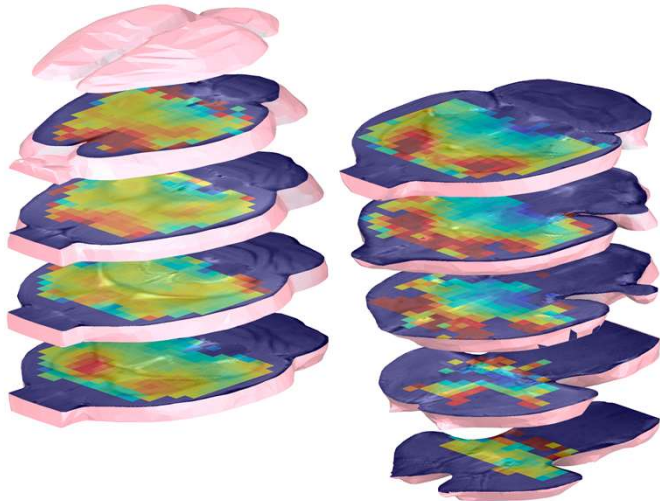
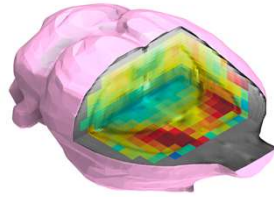


CIBM.CH

cristina.cudalbu@epfl.ch

B Alves, et al, NMR Biomed, 2024; D Simicic et al, NMR Biomed 2025

3D METABOLIC MAP



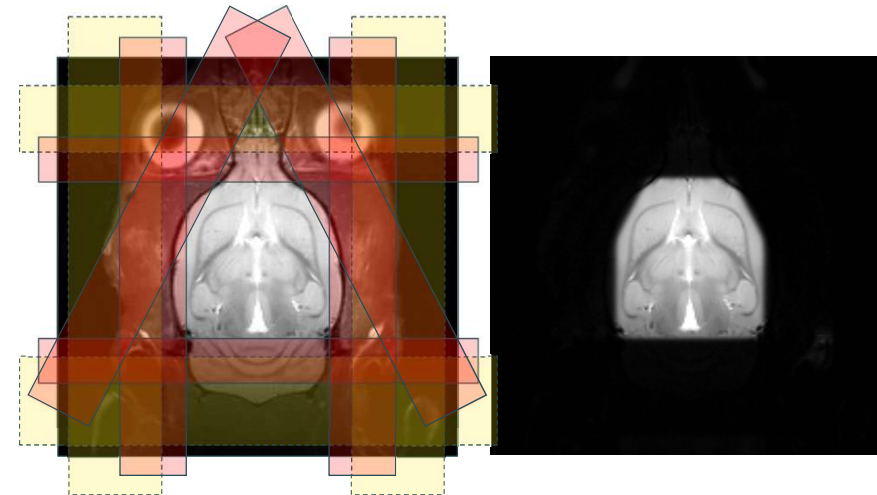
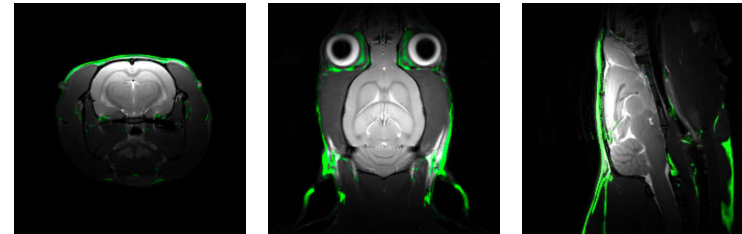
- Time – CS (AF=4, 119min→28min), 1.19 μ L to 0.59 μ L
- PSF & Resolution
- Lipid contamination -- Saturation bands
- Post processing
- ...



B Alves





T Le



MRS4Brain Toolbox

Menu MRSI SVS DWS

Data management

Bruker data folder

Result folder

Study name
31102023_FullySampled_HomeFilter

Processing steps

3D MRSI Number slices

Lipid suppression Fillgaps

Denoising: None

Reconstruction: Cartesian

Data specific

9.4T (for MRI) Reco. Nb



Experiment number folder

PDF document

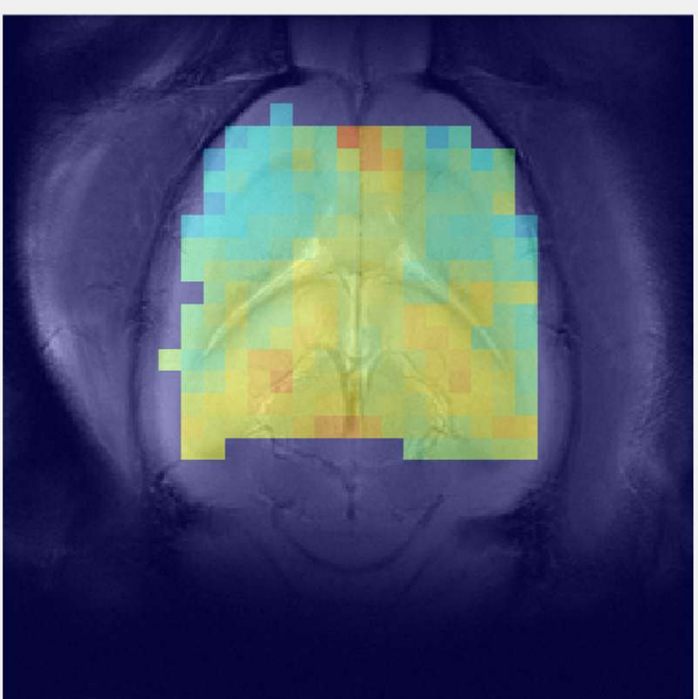
Metabolites Ref Image Slice range

MRI Slice	Number
MRI central slice 1	6

Options

MRSI Analysis



Concentration, Cr+PCr

14
12
10
8
6
4
2
0

Show Results

Job0 Recon.

Slice: Custom regions

Region: Whole Brain




Side: L+R




Concentrations

Metabolite: Ins

Relative

Overlap:

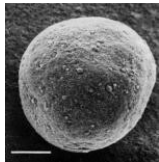


CONCLUSION

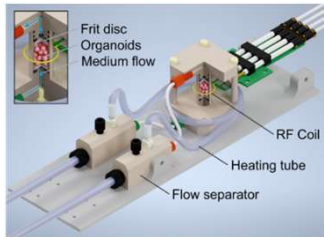


- Novel multimodal imaging approaches and cutting-edge technologies
 - Allow to study different aspects of brain metabolism and structure in type C HE in the adult and developing brain
 - Available @ CIBM PCI EPFL
- **Differential brain regional vulnerability** to the disease → **cerebellum** showing the strongest changes
- Pivotal role of multimodal approaches combining MRS, MRI, FDG PET, EPR, histology to filling the current gap in our understanding of type C HE.
 - ^1H MRS – brain regional and developmental differences
 - FDG-PET – clear proof of energy dysfunction

TRANSLATIONAL

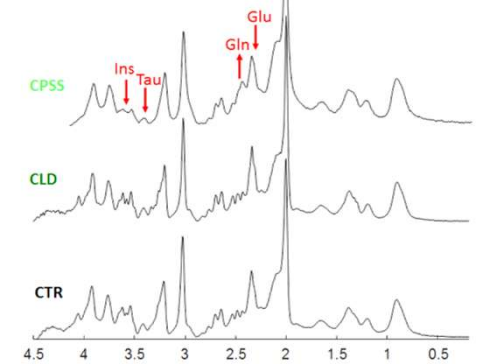
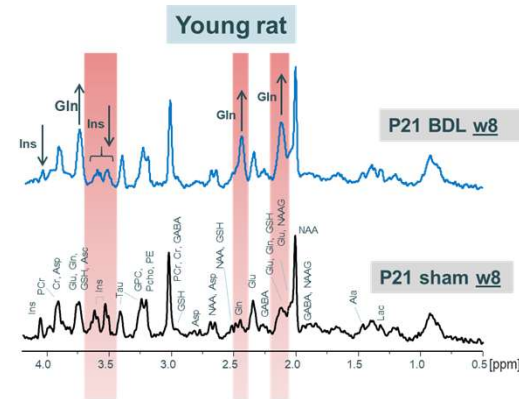
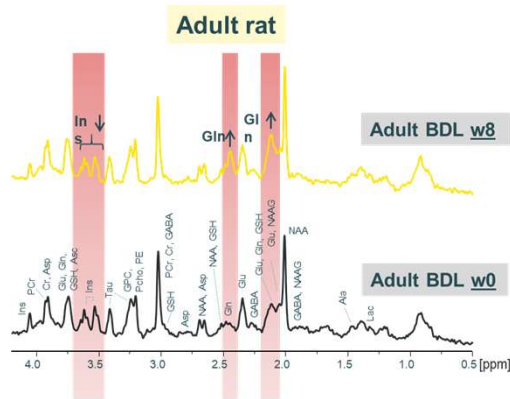
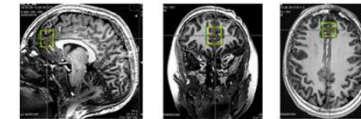
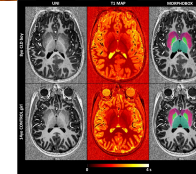
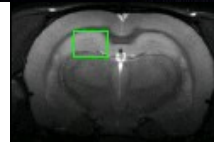


3D organotypic brain cell cultures
Spheres ($\varnothing \Rightarrow 0.5$ mm)
with all types of brain cells.
(bar: 100 μ m)



Courtesy of T Le

Type C HE





ACKNOWLEDGEMENTS



<https://www.epfl.ch/labs/mrs4brain/>

And ALL our collaborators



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HE

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310030_201218 & 207935 & 173222
& 10000465



C I B M . C H

cristina.cudalbu@epfl.ch



THANK YOU FOR YOUR ATTENTION



C I B M . C H