FBEM

Focus on Brain Energy Metabolism
Lactate Shuttle
and Clinical Applications

Scientific symposium

Bordeaux, July 17-18, 2025

Domaine du Haut-Carré
43 Rue Pierre Noailles
33400 Talence

The world's leading experts in cerebral energy metabolism gather

Members of the organizing committee

Anne-Karine Bouzier-Sore
Clémence Faure
Aude Panatier
Alexandra Prévot
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Members of the scientific committee

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The brain's energy metabolism has traditionally focused on the complete oxidation of glucose to carbon dioxide, a well-established process involving glycolysis and oxidative phosphorylation. However, this paradigm has recently been challenged by studies exploring the complexity of interactions between different brain cells, particularly neurons and glial cells.

A major turning point in understanding this topic occurred in 1994 when Pellerin and Magistretti, both prominent figures and invited speakers at our conference, introduced the innovative concept of the astrocyte-neuron lactate shuttle (ANLS). This scientific breakthrough highlighted that astrocytes, previously regarded as mere support cells for neurons, also play a crucial role in glucose metabolism. According to the ANLS model, astrocytes absorb glucose through specific transporters, metabolize it into lactate via glycolysis, and release this lactate for use by neurons as an energy substrate during oxidative phosphorylation.

Recent research has deepened our understanding of the role of the ANLS in neuronal activity, reinforcing the idea that this pathway alters our classical concept of exclusive glucose consumption by neurons. This evolution in knowledge has sparked growing interest, as evidenced by contemporary scientific debates within the neuroenergetics community.

It is essential to continue exploring the underlying mechanisms of brain activity to enrich our understanding of neuroenergetics and develop new therapeutic approaches to address neuropathologies. The two days of conferences we are offering represent a unique opportunity to bring together the world’s leading specialists, thus fostering a fruitful exchange of ideas and essential expertise in this promising field. This conference therefore addresses a critical need to advance research on brain energy metabolism and stimulate therapeutic innovation.

Program July 17th

8:30 – Opening - Welcoming remarks
Anne-Karine Bouzier-Sore, Aude Panatier, Hélène Roumes

Neuron / astrocyte metabolic interactions and exchanges (Chair H. Roumes)

9:00 – Luc Pellerin (IRMETIST U1313, Poitiers, France)
Neuronal and Astroglial Lactate Transporters: Regulation and Roles in Hippocampal-Dependent Learning and Memory Performance

9:30 – Rosa Chiara Paolicelli (Department of Biomedical Sciences, Lausanne, Switzerland)
Focus on Lactate in the Control of Microglial Function

10:00 – Vanja Tepavcevic (University of Valencia, Spain)
Metabolic Support for Myelin Maintenance and Repair: The Role of Monocarboxylates and Their Transporters

10:30 – 11:00 Coffee break

11:00 – Aude Panatier (Neurocentre Magendie, Inserm U1215, Bordeaux, France)
Glucose and Lactate: From Basal Synaptic Transmission to Neuron Excitability

11:30 – Felipe Barros (Centro de Estudios Científicos - CECs, Valdivia, Chile)
Mitochondrial Lactate: a New Player in Energy Metabolism

12:00 – Anne-Karine Bouzier-Sore (CRMSB UMR5536, Bordeaux, France)
Metabolic Interactions Between Neurons and Astrocytes: From Brain Activation to Neuroprotection

12:30 – 14:00 Lunch

Students and young researchers' communications (Chair A. Panatier)

14:00 – 15:30 Students and young researchers' presentations & flash posters (part 1)

Probing Transient Changes in Intracellular-Extracellular Lactate Distribution in the Mouse Brain during Intravenous Lactate Infusion Using Diffusion-Weighted MR Spectroscopy
S. Malaquin *et al.*

The Monocarboxylate Transporter MCT1 Is on-Board of Axonal Vesicles and Uploads Lactate Produced by Vesicular Glycolysis: Consequences for Axonal Transport and Neuronal Signalling
A. Procès *et al.*

Chemogenetic Stimulation of Mature Oligodendrocytes Drives Myelin-Axon Metabolic Coupling and Prevents Axonal Damage
A. Palma *et al.*

Exploring Brain Glucose Metabolism in Multiple Sclerosis: a Deuterium Metabolic Imaging Study
A.S. Khan *et al.*

GLUT1 Deficiency Syndrome: New Horizon
L. Dayraut *et al.*

Flash Poster : Gycogen-Derived Lactate Accelerates Tissue Repolarization during Spreading Depolarization
S. Chen *et al.*

15:30 – 16:00 Coffee break & Poster session

16:00 – 17:30 Students and young researchers' presentations & flash posters (part 2)

Investigating Hub Homeostasis Alterations in Focal Epilepsy Using 7T Sodium and Diffusion MRI
L. Gauer *et al.*

Associations between Cognitive Performance and Brain Metabolism in Individuals with Long-COVID
A.P. Bornes da Silva *et al.*

Lactate: A Promising Therapeutic Approach in the Context of Neonatal Hypoxia-Ischemia
I. Omar *et al.*

Isocaloric Time-Restricted Feeding to Fight Aged-Associated Behavioral Anomalies by Western Diet
D. Passaro *et al.*

Characterization of a New Mitochondrial Disease Associated with SLC25A2/ANT2 Loss of Function
C. Berges *et al.*

Flash Poster: The Role of GLUT3 in Neuronal Energy Metabolism and Cognitive Functions Involving the Rat Somatosensory Cortex
M.A. Zkim *et al.*

17:30 – Poster session

18:30 Wine and cheese & Poster session

POSTERS

1. **ALS May Be a Disease Arising From Human Evolution to Run, via Gangliosides and Lactate: Therapeutic Opportunities** - M. Spedding
2. **Altered Neuronal Lactate Dehydrogenase A Expression in Mice Results in Changes to Spatial Memory and Lipid Droplet Formation Depending on Sex and Age -** M. Courchesne
3. **Lactate Fuels TCA Cycle Flux and Modulates Mitochondrial Function in Microglia** - K. Monsorno
4. **Effects of a Ketogenic Diet on Neuronal and Astrocytic Metabolism in the Mouse Brain: a Two-Photon FLIM Study** - R. Meister et al.
5. **Phenotypical Alterations in Mice Deficient in Astrocytic Mitochondrial Complex I** - M.L. Hidalgo López
6. **Deletion of MonoCarboxylate Transporter 1 in myeloid cells favours glioblastoma development** - S. Lillo
7. **Probing Metabolic Tuning of Neurovascular Coupling by Multimodal Imaging and Optogenetics** - C. Lupiet
8. **The Role of Glucose and Lactate to Sustain Basal Synaptic Transmission and Excitability** - J. Garcia-Ruiz
9. **The Synthetic Cannabinoid URB447 Promotes Neuroprotection in a Neonatal Rat Model of Hypoxic-Ischemic Brain Injury** - M. Chillida
10. **Astrocyte Metabolism as an Epigenetic Regulator of Neural Functions During Cognitive Decline** - M. Antequera
11. **Modeling Neurovascular Coupling** - L. Benyakar
12. **Eco-Friendly Grape Polyphenols Offer Neuroprotection in Neonatal Hypoxia-Ischemia** - P. Goudeneche
13. **Unravelling the Role of Lactate Produced by Axonal Vesicles on Axonal Transport and Neurotransmission** - B. Nicolas
14. **GluCEST as a Translational Biomarker of Synaptic Dysfunction in Alzheimer's Disease** - E.G. Senneset

Program July 18th

Metabolic Interplay Between Neurons and Astrocytes: Implications for Neuroprotection (part 1) (Chair A-K. Bouzier-Sore)

9:00 – Pierre Magistretti (GliaPharm SA, Geneva, Switzerland)
Neuron-Glia Metabolic Coupling Mediated by Lactate: Relevance for Neuroenergetics, Plasticity and Pathology

9:30 – Michèl Willemsen (Department of Pediatric Neurology, Amalia Children's Hospital, Nijmegen, The Netherlands)
Glucose Transporter 1 Deficiency Syndrome: Disease Mechanisms and Therapeutic Perspectives

10:00 – Nikki Robertson (University of Edinburgh, Edinburgh, United Kingdom)
Neonatal Brain Protection and the Use of Brain Lac/NAA in MRS as a Surrogate Outcome Marker

10:30 – 11:00 Coffee break

11:00 – 12:30 Round table: meeting between scientists and physicians (part 1) (Chair F. Villéga)

12:30 – 14:00 Lunch & discussion around the posters

Metabolic Interplay Between Neurons and Astrocytes: Implications for Neuroprotection (part 2) (Chair L. Pellerin)

14:00 – Johanne Egge Rinholm (Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway)
Cell-Type Specific Responses to Ischemic Brain Injury: From Mouse Models to Human Organoids

14:30 – Eduardo Zimmer (UFRGS, Porto Alegre, Brazil)
About Astrocytes in Alzheimer's Disease.

15:00 – Thomas Daubon (IBGC, UMR 5095, Bordeaux, France)
Lactate Shuttle between Glioblastoma Cells and Neurons: a Cancer Neuroscience Case

15:30 – 16:00 Coffee break

16:00- 17:00 Round table: meeting between scientists and physicians (part 2) (Chair F. Villéga)

17:00 – 17:30 Award ceremony and closing of the scientific symposium

Probing Transient Changes in Intracellular-Extracellular Lactate Distribution in the Mouse Brain during Intravenous Lactate Infusion using Diffusion-Weighted MR Spectroscopy

Sophie Malaquin, Julien Valette, Celine Baligand
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The distribution of lactate among neurons, glial cells, and the extracellular space is fundamentally important for brain function1. Detecting transient changes in lactate distribution would be invaluable to study lactate dynamics. Diffusion-weighted MR spectroscopy (dMRS) can be used to non-invasively assess lactate intracellular-extracellular compartmentation in the brain at equilibrium[2], but long measurement times may hamper detection of any transient changes. Here, we show that it is possible to non-invasively detect transient changes in lactate compartmentation induced by intravenous lactate infusion.

We scanned six mice at 11.7T with a cryoprobe, and by using dMRS and modeling the data acquired, and we were able to non-invasively capture transient changes in lactate distribution in the brain with a time resolution of 6 minutes. We successfully demonstrated that changes in lactate concentration and compartmental distribution can be achieved in the brain through intravenous injection, and maintained to a steady state during a lactate infusion. With more acquisitions in the low b-values range, it may be possible to estimate the lactate vascular fraction and kinetics of lactate exchange between compartments, which would be invaluable to better understand lactate's role in brain function.

The Monocarboxylate Transporter MCT1 Is on-Board of Axonal Vesicles and Uploads Lactate Produced by Vesicular Glycolysis: Consequences for Axonal Transport and Neuronal Signalling

Anthony Procès[1], Barbara Nicolas[1], Béatrice Blot[1], Marta Prieto[1], Frédéric Saudou[1#]
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Neurotransmission involves the precise transport of vesicles from the cell body to the synapse, a process known as fast axonal transport, which relies on molecular motors and energy. Previous research has shown that glycolytic enzymes on vesicles provide the necessary energy for this transport, independent of mitochondria. Recently, we discovered that LDHA on brain vesicles converts pyruvate to lactate and recycles NADH to NAD^+, sustaining glycolysis indicating a dependency on a vesicular Warburg effect, but the role of the produced lactate remains unknown.

Using mass spectrometry and immunochemistry, we reveal that MCT1, which transports lactate across membranes, is present on axonal vesicles. Metabolomic profiling identified lactate within these vesicles, and biochemical assays confirmed that lactate loading into vesicles is MCT1dependent. Given lactate's emerging non-metabolic roles in neurotransmission, we investigated how neuronal activity affects axonal transport and lactate production. Using reconstituted neuronal circuits in microfluidic chips and an ultrasensitive lactate sensor, we found that neuronal activity significantly increases lactate production on vesicles within axons. We are now exploring how this lactate production and uptake influence axonal transport and postsynaptic signaling pathways. Overall, this research identifies a new source of lactate in neurons and suggests a novel regulatory mechanism for neurotransmission.

Chemogenetic Stimulation of Mature Oligodendrocytes Drives Myelin-Axon Metabolic Coupling and Prevents Axonal Damage

Ana Palma[1,2], Marina Bosch-Juan[1,2], Stefano Calovi [1,2], Carla Peiró[1,2], Izaskun Buendía[1,2], Carlos Matute[1,2,3], Alberto Pérez-Samartín[1,2,3], María Domercq[1,2]

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Oligodendrocytes produce myelin and provide metabolic support to axons through lactate release. While experience and neuronal activity drive dynamic changes in myelination during development and adulthood, this plasticity has been attributed to newly-formed oligodendrocytes. The role of mature oligodendrocytes (mOLs) to such remodeling remains poorly understood. To address this, we generated a transgenic mouse line with CreERT2-lox technology, overexpressing the hM3Dq DREADD receptor under the Plp promoter, enabling selective chemogenetic activation of mOLs. Chronic in vitro hM3Dq stimulation enhanced myelination, while in vivo activation produced modest changes in myelin structure but significantly shortened nodes of Ranvier, increasing conduction velocity across callosal axons. Acute stimulation boosted oligodendrocyte metabolism, increasing glycolysis, lactate production, and its release. This enhanced metabolic coupling mantained axonal function under high-frequency stimulation and prevented axonal damage secondary to oxygen-glucose deprivation. We also tested mOLs chemogenetic stimulation to promote remyelination and protect axons under demyelinating, which ameliorated motor symptoms in experimental autoimmune encephalomyelitis and prevented axonal and oligodendrocyte damage. These findings demonstrate that our chemogenetic model offers a valuable tool to elucidate the contribution of mOLs to myelin remodeling in physiological and pathological conditions, and reveals a novel role of myelin-axon lactate shuttle in axonal protection in demyelinating disorders.

Exploring Brain Glucose Metabolism in Multiple Sclerosis: A Deuterium Metabolic Imaging Study

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Multiple sclerosis (MS) stems from an autoimmune response causing an inflammatory attack leading to neurodegeneration, including demyelination and axonal damage. Conventional MRI can measure structural changes using FLAIR to detect focal lesions associated with areas with inflammation. However, a critical aspect of MS is smouldering inflammation, which contributes to symptomatic deterioration even in the absence of acute relapses or new lesion formation. Metabolic imaging can enable a unique perspective into MS by measuring the altered cellular metabolism that may be sensitive to smoldering associated worsening. Deuterium Metabolic Imaging (DMI) is an emerging metabolic imaging technique in which 2H-labelled glucose is orally administrated and imaged using MRI. In doing so, glucose uptake and downstream metabolic conversion to Glx (glutamate and glutamine) and lactate can be measured.

In this proof-of-concept study, DMI was applied to patients with relapse-remitting MS in a clinical MRI system to validate its ability to measure altered metabolism. 7 people with MS and 4 healthy controls were imaged. Within the MS patient cohort increasing lesion count correlated significantly with increased Glx and Lactate (R^2 = 0.6680, p = 0.0458 and R^2 = 0.6719, p = 0.0470, respectively). These findings highlight DMI to probe metabolic dysregulation linked to neurodegeneration.

GLUT1 Deficiency Syndrome: New Horizon

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The GLUT1 deficiency syndrome (GLUT1DS) is a rare systemic condition with a pediatric onset, leading to drug-resistant epilepsy, neurodevelopmental and movement disorders. The GLUT1 transporter facilitates the transport of glucose from the bloodstream to the central nervous system (CNS). The brain is an organ with high energy requirements and consumes its energy in the form of glucose. This transport is therefore essential for the CNS. Patients with GLUT1DS experience a significant reduction in cerebral energy supply. The only currently available therapy is a ketogenic diet, which is proportionally low in carbohydrates and high in lipids. However, this diet does not alleviate all symptoms, is ineffective for about 25% of patients and represents a major challenge for families. To explore new therapeutic avenues, our team has developed a new rodent model of GLUT1DS, generated by CRISPR-Cas9 in rats (GLUT1+/-). It represents a valuable tool for identifying innovative therapies aimed at improving both therapeutic management and patients' quality of life. The multimodal characterization of this new model is currently underway. Finally, in conjugation with this preclinical phase, a retrospective, observational clinical study is being conducted on GLUT1DS patients. This study will provide scientific evidence to support the implementation of a future therapeutic clinical trial.

Flash Poster: Glycogen-Derived Lactate Accelerates Tissue Repolarization during Spreading Depolarization

Shuting Chen[1], Baptiste Balanca[1], Andrei Sabac[2], Melissa Hexter[1], Stéphane Marinesco[1]

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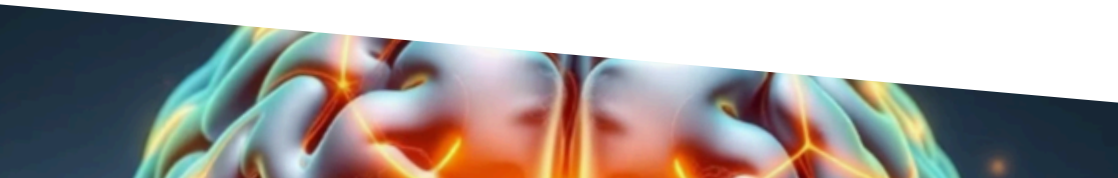
Glycogen stores are the only energy reserve in the brain. They are present in astrocytes and preferentially release lactate upon neuronal stimulation, memory formation, or pathological conditions such as ischemia or epilepsy. This glycogen-derived lactate can be taken up by neurons to provide an energy boost. However, the metabolic pathway by which glycogenderived lactate provides energy to brain cells and the time needed for glycogen recruitment after an energy demanding stimulus are still poorly understood. Cortical spreading depolarization (SD) is a wave of near-complete depolarization of neurons and glial cells propagating through the cortex. Tissue repolarization after SD is energy-demanding and represents a strong metabolic challenge, providing a model for investigating the recruitment of glycogen stores. Here, the depolarization-repolarization process was monitored using electrocorticography (ECoG), and glucose, lactate and oxygen concentrations were quantified using minimally invasive microelectrode biosensors developed in our laboratory. Glycogen phosphorylase inhibitor 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) was locally administrated into rat brain to block glycogenolysis. DAB administration prolonged SD duration from 25 ±1.3 s to 34 ±1.3 s ($p<0.001$, $n=12$), and glucose and oxygen consumption. SD induced a wave of lactate release that was reduced by 42% by DAB, with significantly less lactate detected in the interstitial fluid 42s after the start of the SD. Intravenous lactate supplementation rescued the duration of repolarization in the presence of DAB. These data indicate that glycogen stores are hydrolyzed during SD, to produce lactate that is released in the interstitial fluid and used as energy source to accelerate tissue repolarization. Interestingly, utilization of glycogen-derived lactate did not increase oxygen consumption, suggesting utilization in a non-oxidative pathway, for example the malate-aspartate shuttle.Overall, these results indicate that astrocytic glycogen stores can be recruited within seconds of an energy-demanding stimulus to release lactate into the interstitial fluid, and that this glycogen derived lactate accelerates tissue repolarization after an SD without oxygen consumption.



Investigating Hub Homeostasis Alterations in Focal Epilepsy using 7T Sodium and Diffusion MRI

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Brain hubs are regions vulnerable to the energy deficits in brain disorders. In focal epilepsy, alterations in sodium homeostasis have been observed and may reflect such deficits. We hypothesize that the metabolic demands of hub regions produce a distinct ionic profile. Using sodium MRI, we investigated whether we could detect this profile and how it is altered in focal epilepsy.

Sixty-four patients with drug-resistant focal epilepsy and 23 healthy controls underwent anatomical, diffusion-weighted, and sodium imaging on a 7 Tesla MRI scanner. Patients underwent pre-surgical work-up, including stereo-electroencephalographic recordings. Multimodal coregistration allowed us to link graph metrics of structural connectivity to epileptogenicity and sodium parameters.

In both groups, hubs showed higher total sodium concentration (TSC) than non- hubs, with no hub- related difference in sodium signal fraction (f, a proxy for intracellular sodium homeostasis). Compared to controls, patients exhibited globally elevated TSC in both epileptogenic and non- epileptogenic zones, equally in hubs and non- hubs, while f increased only within epileptogenic zones, regardless of hub status. These results replicate prior observations of whole- brain TSC elevation and local f increases in focal epilepsy.

We propose that TSC reflects widespread microstructural alterations, whereas f could reflect homeostatic disruptions specific to epileptogenic regions.

Associations between Cognitive Performance and Brain Metabolism in Individuals with Long-COVID

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Background: Long-COVID has been associated with persistent neurological symptoms. Exploring their link to brain metabolism and cognitive reserve may clarify post-infection effects. This study examined associations between neuropsychological performance and brain metabolism in Long-COVID and control individuals, considering high (>11 years) vs. low (<11 years) education.

Methods: We included 116 participants aged >50 from Porto Alegre-Brazil, divided into four groups: high-education controls (CHE, n=29), low-education controls (CLE, n=27), high-education Long-COVID (Cov-HE, n=30), and low-education Long-COVID (Cov-LE, n=30). All underwent MMSE, GAD-7, PHQ-9 assessments and [18F]FDG-PET brain imaging, normalized by global mean. Voxel-wise linear regressions were performed adjusting for covariates and corrected by random field theory ($p<0.001$).

Results: Positive and negative associations were observed between test scores and brain glucose metabolism. Anxiety symptoms were associated with metabolism in the superior frontal (CHE) and superior temporal gyrus (CHE, Cov-LE). Cognitive scores showed associations in the middle temporal (CHE), superior temporal/occipital gyrus

(CLE), parietal/frontal lobes (CLE, Cov-LE) and caudate nucleus (Cov-LE). Depressive symptoms were associated with metabolism in frontal regions (CHE, CLE, Cov-HE) and cerebellum (CLE).

Conclusion: Emotional and cognitive symptoms in Long-COVID are linked to distinct neurometabolic patterns, modulated by educational level, suggesting a role for cognitive reserve in Long-COVID brain function.

Keywords: Long-COVID, brain metabolism, cognitive reserve.

Lactate: a Promising Therapeutic Approach in the Context of Neonatal Hypoxia-Ischemia

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Since the discovery of the astrocyte-neuron lactate shuttle in 1994, lactate has been considered a preferential neuronal energy substrate. Our team explored its neuroprotective potential in neonatal hypoxia-ischemia (NHI), a major cause of neonatal morbidity. Currently, hypothermia is the only approved treatment but is effective in only ~50% of cases. Using a rat model, we aimed to (1) optimize hypothermia duration, (2) compare the effects of lactate, hypothermia, and their combination, and (3) assess the impact of sodium L-lactate infusion on blood parameters in preterm infants.

Preclinical study: 7 groups of postnatal day 7 rats were examined: sham, NHI with normothermia, NHI with hypothermia (2, 3, or 5 hours), lactate post-treatment, and combined hypothermia (2 h) with lactate. Brain lesion volumes were quantified using diffusion-weighted MRI at 3 h, 48 h, and 23 days post-NHI. Behavioral tests at adulthood and microglial activation (via Iba1 immunostaining) were conducted. Clinical study: 60 preterm infants (30 received sodium L-lactate; 30 received NaCl) were monitored for blood pH, lactate, bicarbonate, sodium, chloride, and base excess before, during, and after infusion.

Preclinical study: 2 h of hypothermia reduced lesion volume and improved behavioral outcomes. Lactate, alone or with hypothermia, further enhanced neuroprotection. Clinical study: Sodium L-lactate infusion did not increase lactatemia and facilitated faster pH normalization than NaCl.

Post-NHI lactate treatment offers promising neuroprotection and shows translational potential in neonatal care.

Isocaloric Time-Restricted Feeding to Fight Aged-Associated Behavioral Anomalies by Western Diet

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Consumption of fat-rich food, such as that in the Western diet, contributes to brain aging, which may be alleviated by lifetime dietary healthy habits including time-restricted feeding. However, direct proof of concept of this statement is lacking. To address this issue, here we used 3 groups of C57BL/6 male mice (n=50/group), which were divided into 4 experimental conditions resulting from crossing two different feeding regimes, namely Ad-Libitum (AL) or Isocaloric Time-Restricted (ICTR), under two types of diet, namely Standard (SD) or HighFat Diet (HFD). At the age of 6 months, mice were switched to one of these conditions for 3 (mature adult), 6 (middle-age), and 12 (old) more months, respectively.

Our results show different metabolic profiles in the 4 groups. At all age stages, mice under AL-HFD showed glucose intolerance, higher post-fasting ketone bodies blood level, and higher amount of liver lipid droplets. Furthermore, premature impairment in locomotor activity, short-term memory, and anxiety-like behavior was observed. ICTR feeding prevented the metabolic and cognitive deterioration induced by SD feeding. These results suggest that ICTR feeding may preserve healthy metabolism and higher-order cognitive behaviors during aging in individuals fed under western diet.

Characterization of a New Mitochondrial Disease Associated with SLC25A2/ANT2 Loss of Function

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More than 900 genes have been identified as monogenic causes of developmental delays associated with epilepsies. A genetic etiology can now be established in nearly 50% of patients through next-generation sequencing technologies. However, a significant proportion of patients remain undiagnosed, highlighting persistent gaps in our understanding of these syndromes. Here, we report the case of a male patient who presented in early childhood with severe absence epilepsy, followed by features consistent with autism spectrum disorder, mild psychomotor delay (delayed walking and speech), and intellectual disability. Brain MRI was unremarkable, and there was no relevant family history or consanguinity. Genetic investigations identified a 232 kb deletion at Xq24, encompassing the entire SLC25A5 gene, which encodes ANT2, a mitochondrial adenine nucleotide translocase involved in ADP/ATP exchange across the inner mitochondrial membrane. Family screening revealed that the patient's mother and sister are asymptomatic carriers of the deletion, with skewed X-inactivation (91–8% and 79–21%, respectively), whereas other maternal relatives tested negative.

The contribution of the SLC25A5 deletion to the observed phenotype remains to be characterised. The objective of this study is to elucidate its biological impact. Given the known role of ANT2 in mitochondrial energy metabolism, we hypothesize a link between SLC25A5 deletion and mitochondrial dysfunction contributing to the observed neurodevelopmental phenotype. To explore this, we performed western blot analyses of mitochondrial respiratory complexes, Seahorse assays to assess cellular respiration, 13C-glucosebased NMR spectroscopy for metabolic flux analysis, and ATP/ADP quantification.

Our findings support a role for SLC25A5 as a novel candidate gene involved in neurodevelopmental disorders. ANT2 deficiency may impact brain energy metabolism, potentially contributing to the underlying pathophysiological mechanism.

Flash Poster: The Role of GLUT3 in Neuronal Energy Metabolism and Cognitive Functions Involving the Rat Somatosensory Cortex

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Brain energy metabolism has gained renewed interest due to its crucial role in normal brain function (learning and memory) and in neuropathological processes (e.g. Alzheimer's disease). Understanding how the energy demands of neuronal activity are met is essential for deciphering both physiological and pathophysiological processes. Energy substrate transporters, such as monocarboxylate and glucose transporters, are critical components of neuronal energy supply. Our study aimed to evaluate the impact of reducing the expression of the neuronal glucose transporter GLUT3 on various metabolic parameters in vitro, as well as on certain cognitive functions in vivo.

A first step was conducted in vitro using primary cultured neurons. We selected the most effective shRNA sequence (out of two tested) to reduce GLUT3 expression while preserving the expression of the neuronal lactate transporter MCT2. We also assessed the vector's toxicity to determine the optimal dose-response combination. Finally, we evaluated the impact of GLUT3 downregulation on several neuronal energy parameters in vitro. The second step was carried out in vivo to assess the effect of reduced GLUT3 expression on cognitive functions associated with the primary somatosensory cortex (S1BF). For this purpose, we used a textured novel object recognition (tNOR), using the whisker-to-barrel system, to evaluate the role of the neuronal GLUT3 in memory formation within the S1BF. Memory formation independent of the S1BF was evaluated using a visual task.

In vitro results show that reducing GLUT3 by approximately 80% at the protein level had no significant effect on several key parameters of neuronal energy metabolism (ATP production, mitochondrial respiration, glycolysis) or on glutathione implicated in the

pentose phosphate pathway. In vivo, the reduction of GLUT3 by approximately 38% at the protein level in the S1BF region had no impact on the animal's ability to perform a memory task involving the S1BF. This result contrasts with the memory impairment observed when MCT2 was downregulated with a similar approach in the same cortical region.

Our work suggests that i) GLUT3 expression in vitro is not a limiting factor for sustaining neuronal energy metabolism; and ii) in vivo, neuronal GLUT3 expression is less critical than MCT2 for supporting cognition and brain activation during tasks involving the whisker-tobarrel system and the somatosensory cortex.

Poster 1 : ALS May Be a Disease Arising From Human Evolution to Run, via Gangliosides and Lactate: Therapeutic Opportunities

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Evolution of hominins was accelerated 3-2.5Mya, by cytidine monophospho-Nacetylneuraminic acid hydroxylase (CMAH) becoming a pseudogene, probably after a pathogenic infection, changing the sialome, lipid metabolism, brain development and neuromuscular junctions (NMJs). This was when hominins evolved to run in Africa and develop bigger brains. CMAH by hydroxylating N-acetylneuraminic acid (Neu5Ac), yielding Nglycolylneuraminic acid (Neu5Gc) ensures that Neu5Ac is human specific. Deletion of CMAH in mice allows them to run for longer (50%) with more efficient oxygen use. GM1 is a neurotrophin binding to TrkA and TrkB receptors. GM1 is lost from NMJs at the beginning of denervation in SOD1G86R and TDPQ331K mice, probably because of a 10-fold increase in glucosylceramidases (non-lysosomal GBA2), and thereby a critical hub for viral infection and also for ALS and NMJ stability. A GBA2 inhibitor, ambroxol, is in phase II for ALS (NCT05959850). GM1 may therefore be critical for ALS and human evolution.

At the same time human lipid and glucose metabolism changed to support human endurance; changes in lipid metabolism are marked in ALS. Recently the appreciation of lactate as a major body/brain fuel, and critical for athletic performance, with the best cyclists maintaining blood lactate at 3mM at >400 watts for sustained periods. Lactate production in even newly diagnosed ALS patients is severely compromised and is a marker of disease progression. GM1 has major effects on lactate production from astrocytes (Magistretti).

Poster 2 : Altered Neuronal Lactate Dehydrogenase A Expression in Mice Results in Changes to Spatial Memory and Lipid Droplet Formation Depending on Sex and Age

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The cellular mechanisms that underly learning and memory consolidation in the brain are bioenergetically demanding. Since neuronal glucose utilization declines with age, the brain relies on alternate metabolites such as lactate and lipids as fuel sources. The improper processing of these metabolites may underlie memory deficits typically observed in later life. Lactate production is primarily governed by lactate dehydrogenase-A (LDHA) activity, the rate-limiting enzyme catalyzing pyruvate to lactate conversion. The present study suggests that neuronal-specific LDHA levels are elevated with age. Additionally, the effects of neuronal-specific ldha induction and knockout on spatial learning and memory was examined using the Morris water maze and object location tasks. Elevated neuronal-generated lactate promoted learning in young female mice, while memory impairments were observed with aged male neuronal ldha-induction mice. In contrast, spatial contextual memory was improved in old ldha knockout mice compared to age-matched controls. Levels of perilipin2, which maintains lipid droplet (LD) integrity to prevent free-fatty acid toxicity, were reduced within hippocampal neurons of induction mice, but increased in knockout mice compared to controls. These findings suggest that elevated neuronal lactate production may interfere with protective LD formation to preserve memory in older animals, thus providing a novel perspective on the role of lactate and lipid processing on memory across lifespan.

Poster 3 : Lactate Fuels TCA Cycle Flux and Modulates Mitochondrial Function in Microglia

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Microglia, the tissue-resident macrophages of the central nervous system, actively participate in brain development and homeostasis maintenance. These cells are emerging as highly metabolically flexible, able to oxidize a variety of nutrients to meet their energy demand and sustain their cellular activities. We have previously demonstrated that microglia-specific knock out (cKO) of MCT4, a high-affinity lactate transporter, leads to significant defects in microglial phagocytosis, associated with impaired synapse remodelling, increased neuronal excitability, and long-lasting anxiety-like behaviour. However, it is still unclear whether lactate is efficiently metabolized by microglia, and what the functional consequences of its utilization may be in specific contexts.

Here, using a combination of mass spectrometry, high-resolution respirometry, patch clamp and confocal microscopy, we confirmed that extracellular lactate is imported by microglia, and it directly regulates TCA cycle fluxes and mitochondrial activity. In addition, we described a specific role for lactate in altering cellular as well as mitochondrial membrane potential, which is strictly dependent on lactate oxidation. Finally, enhancing lactate availability in vivo, we provided evidence of acute effects on microglia metabolism and microglia-synapse interactions.

Poster 4 : Effects of a Ketogenic Diet on Neuronal and Astrocytic Metabolism in the Mouse Brain: A Two-Photon FLIM Study

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Ketogenic diets (KDs) protect against epileptic seizures and shows benefits in metabolic, neurodegenerative and even psychiatric diseases. The high fat intake raises blood ketones (notably BHB), which serve as alternative energy substrates for different organs. We monitored blood BHB, glucose and lactate during an alternating KD to assess their systemic dynamics.

The brain is an avid consumer of ketone bodies. Techniques such as PET and fMRI provide insight into the neurometabolic impact of a KD but lack the spatial resolution necessary to distinguish different cell types. To evaluate metabolite levels and fluxes in the mouse cortex at the single-cell level, we combine genetically encoded sensors with two-photon fluorescence lifetime imaging (FLIM). This quantitative technique allowed us to assess how a KD impacts glucose levels and the redox ratio of both neurons and astrocytes in the awake mouse. Using acute brain slices, we were also able to employ pharmacological protocols to measure the glycolytic rate in both cell types from mice on a KD and directly contrast the glucose and redox states to the in vivo condition.

Overall, our work shows a cell-specific and quantitative effect of a KD on brain metabolism, complementing information from whole-brain studies.

Poster 5 : Phenotypical Alterations in Mice Deficient in Astrocytic Mitochondrial Complex I

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Energy metabolism is regulated by the availability of oxygen and substrates and other factors, such as reactive oxygen species (ROS). One of the ROS production main sites is the mitochondrial complex I (MCI). Given the relevant role of MCI in ROS production, we set out to investigate a knock-out of Ndufs2, a central subunit of MCI, to cause the loss of this mitochondrial complex.

To induce Ndufs2 gene deletion, mice were injected with an adeno-associated virus (AAV) expressing Cre recombinase governed under GAFP promoter. Mice weight and food intake were continuously monitoring. One month after Ndufs2 deletion, animals display a marked arrest in weight gain. Finally, three months later, mice die. Previously to death, animals show cognitive and motor alterations without signs of pain or suffer. In parallel with mice behavior, the metabolism of astrocytes from knock-out mice is also disrupted measure oxygen consumption in astrocytes isolated from adult brains. In this sense, we observe a decline in basal respiration, maximal respiration, and spare respiratory capacity in these cells.

Mitochondrial complex I loss, specifically, in astrocytes leads to severe mitochondria dysfunction, resulting in the impairment of the brain metabolism and the mouse cognitive and motor performance and, ultimately, mice death.

Poster 6 : Deletion of MonoCarboxylate Transporter 1 in Myeloid Cells Favours Glioblastoma Development

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Glioblastoma (GB) is the most aggressive brain tumor, with a median survival of less than 15 months after diagnosis. Despite surgical resection and radio-chemotherapy, patients suffer from a high rate of tumor recurrence explained by an enriched immune environment in myeloid cells possessing protumoral properties. GB cells release large amounts of lactate, responsible for immuno-metabolic modifications of immune cells in other cancers. Altogether, TAM abundancy and lactate concentration may impact tumor development and patient's outcome. However, lactate's specific effects on myeloid cell phenotypes and functions within GB tumor microenvironment is poorly understood. In vivo experiments of mouse models deficient for MonoCarboxylate Transporter 1 (MCT1), a lactate transporter in myeloid cells ($Mct1^{\Delta mye}$), show significantly larger tumors compared to WT mice and highlight enriched pro-tumoral TAMs by flow-cytometry in male. Interestingly, histology revealed significantly higher and a tendency towards a higher proportion of pro-tumoral macrophages ($IBA1^{+}$, $ARG1^{+}$) in $Mct1^{\Delta mye}$ mice. In vitro, Bone Marrow-derived macrophages (BMDMs) from WT or $Mct1^{\Delta mye}$ mice showed no differential response when challenge with sodium-lactate, for phagocytosis or co-cultured with mGB2 for tumor cell invasion. Metabolic analysis between WT and $Mct1^{\Delta mye}$ BMDMs is currently under investigation. Together, these results question lactate's role in myeloid cells in glioblastoma development.

Poster 7 : Probing Metabolic Tuning of Neurovascular Coupling by Multimodal Imaging and Optogenetics

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Brain function depends on a constant supply of oxygen and glucose delivered by a dense vascular network. Pyramidal cell activity regulates local blood flow through neurovascular coupling (NVC), and promotes glucose uptake by neurons and astrocytes via neurometabolic coupling (NMC). These processes cause a transient increase in extracellular lactate, which supports energy needs in active brain regions and is essential for cognition and memory. However, excessive lactate can be harmful and is implicated in neurological disorders. Despite its importance, how NVC and NMC are coordinated remains poorly understood. Recent data from our team show that lactate is a key energy source enhancing neuronal firing. Moreover, vasodilator neurons can become vasoconstrictors at high spiking frequencies, possibly to limit excess lactate and maintain balance. This project aims to determine how lactate modulates neuronal activity and NVC using ex vivo brain slices, imaging, and optogenetics. We are measuring lactate's effect on pyramidal neuron activity using whole-cell recordings and calcium imaging. We also assess the impact of lactate on the NVC response induced by the optogenetic stimulation of pyramidal cells, and use pharmacological tools to analyze the underlying mechanisms.

Poster 8 : The Role of Glucose and Lactate to Sustain Basal Synaptic Transmission and Excitability

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The brain represents 2% of body weight but consumes 20% of the body's glucose: 80% is used by neurons, 20% by astrocytes and other glial cells. While neurons were long thought to rely exclusively on glucose via GLUT3dependent uptake, growing evidence highlights an important role for astrocyte-derived lactate as an energy source. Astrocytes, positioned between blood vessels and synapses, take up glucose and convert it into lactate. Lactate is released via MCT1/MCT4 transporters and taken up by neurons through MCT2 to generate ATP. Understanding when and how neurons switch between glucose and lactate remains a fundamental question in brain energetics. Our aim is to determine whether the choice of energy source depends on energy demand. We used a viral approach to downregulate either the neuronal glucose transporter GLUT3, the neuronal MCT2 lactate transporter, or the astrocytic MCT1/MCT4 transporter in the rat somatosensory cortex. During whole-cell patch-clamp recordings, basal synaptic transmission was assessed via miniature excitatory postsynaptic events, and neuronal excitability by firing frequency. Our data indicate that glucose and lactate both regulate neuronal basal synaptic transmission. Regarding excitability, our data indicate that glucose plays a gatekeeper role. These findings reveal distinct roles of glucose and lactate in regulating neuronal functions.

Poster 9 : The Synthetic Cannabinoid URB447 Promotes Neuroprotection in a Neonatal Rat Model of Hypoxic-Ischemic Brain Injury

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Hypoxic-ischemic (HI) brain injury remains a leading cause of neonatal mortality and longterm neurological disability, primarily due to disruptions in brain energy metabolism. The endocannabinoid system has emerged as a promising target for neuroprotection due to its ability to regulate pathophysiological processes such as glutamate excitotoxicity, oxidative stress, and inflammation after HI. Our aim was to evaluate the neuroprotective effect of URB447, a CB1R-antagonist/CB2R-agonist, in a neonatal rat model of HI.

Postnatal day 7 (P7) Wistar rats underwent unilateral ligation of the left common carotid artery followed by 2h of hypoxia ($8\%O_2/92\%N_2$). URB447 (1 mg/kg) was administered 3h after HI. Brain lesion size was assessed by magnetic resonance diffusion-weighted imaging at P7, P9 and P30. Behavioral assessments were performed at P8 (righting reflex), P24 (mNSS) and P27 (open-field). Metabolic changes were evaluated by proton nuclear magnetic resonance spectroscopy at P30.

URB447 administration was associated with a decrease in brain lesion size 48h after HI, better neurological outcomes in all behavioral tests, and improved GABA/Glutamate ratios compared to non-treated HI rats.

In conclusion, our results suggest that URB447 administration, acting as a simultaneous CB1R-antagonist/CB2-agonist, may represent a promising strategy to counteract both structural and functional brain damage after HI brain injury.

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Poster 10 : Astrocyte metabolism as an epigenetic regulator of neural functions during cognitive decline

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In recent decades, increasing life expectancy has led to a growing prevalence of cognitive impairment and related brain diseases. Healthy aging involves metabolic alterations associated with cognitive decline (1). Astrocytes, with direct access to brain vasculature, play a crucial role in brain metabolism by sensing systemic changes and providing metabolic and functional support to neurons. They produce lactate, acetyl-CoA and β-hydroxybutyrate –key metabolites that serve as energy substrates or metabolic precursors to sustain cognitive performance (2, 3). These metabolites can also induce post-transcriptional histone modifications (PTMs) and thereby modulate gene expression in a metabolism-dependent manner (4).

In this context, lifestyle is a modifiable factor with a strong influence on brain metabolism and cognitive performance (5). Our study investigates how aerobic exercise affects metabolismdriven epigenetic modifications of histones in astrocytes.
Preliminary DNA ChIP-Seq analyses in astrocytes isolated from mice subjected to aerobic exercise reveal changes in chromatin acetylation patterns. These alterations correlate with systemic metabolic changes in glucose and fatty acid utilization, along with improved longterm cognitive performance. Our findings suggest a potential link between astrocytic metabolism and cognitive function mediated by epigenetic mechanisms, providing a proof of concept for further research into the molecular basis of age-related cognitive decline.

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Poster 11 : Modeling Neurovascular Coupling

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The brain critically depends on the uninterrupted vascular supply of oxygen and glucose. Cerebral blood flow is locally regulated by neuronal activity, a process referred to as neurovascular coupling (NVC), which optimizes energy delivery to activated brain regions through the coordinated regulation of vasodilation and vasoconstriction. NVC relies on complex interactions between neurons, astrocytes, and blood vessels. Although vasodilation is better understood, the mechanisms of vasoconstriction remain underexplored. To better understand this process, we developed minimal differential equation models to describe the changes in arteriole diameter observed during vasoconstriction induced by different stimuli. This model was successfully fitted to experimental data from mouse brain slices, capturing arteriole contraction dynamics under various conditions.

Specifically, we analyzed vasoconstriction induced by the exogenous application of two vasoconstrictors —Prostaglandin E2 (PGE2) and Neuropeptide Y (NPY). This model not only describes these vascular responses but also enables the estimation of free parameters, ensuring its validity and predictive potency. In particular, it allowed us to estimate a plausible concentration of PGE2 at the arteriolar level that induces vasoconstriction.

By integrating experimental data with theoretical modeling, we offer new insights into the role of PGE2 in NVC and its implications for both physiological and pathological conditions.

Poster 12 : Eco-Friendly Grape Polyphenols Offer Neuroprotection in Neonatal Hypoxia-Ischemia

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Neonatal hypoxia-ischemia (NHI) is a leading cause of perinatal mortality and long-term neurological disabilities. Currently, therapeutic hypothermia remains the only validated treatment, though it is ineffective for a significant proportion of newborns. We recently demonstrated that maternal nutritional supplementation with resveratrol (RSV), a grape-derived polyphenol, provides neuroprotection in a rat model of NHI. This effect is partially mediated by the modulation of genes involved in the astrocyte-neuron lactate shuttle, suggesting an enhancement of cerebral energy metabolism.

However, the clinical translation of RSV is limited by its low bioavailability (<1%). To overcome this limitation, we evaluated a polyphenolic cocktail (RSV, pterostilbene, and ε-viniferin), produced and extracted through green chemistry, with the aim of achieving synergistic effects and improved bioefficacy. Pregnant rats received the supplementation two weeks prior to NHI induction in pups (unilateral carotid artery ligation followed by hypoxia). The HIC group, used as the control for hypoxia-ischemia, received no supplementation.

Brain lesion volumes were assessed using diffusion-weighted MRI. The cocktail significantly reduced lesion volume and the severity of edema (higher ADC values) compared to the HIC group. Moreover, motor and cognitive functions were better preserved and comparable to the Sham group. These findings highlight the enhanced neuroprotective potential of combining polyphenols, supporting the development of plant-based extracts that combine synergy and bioavailability for optimal perinatal neuroprotection.

Poster 13 : Unravelling the Role of Lactate Produced by Axonal Vesicles on Axonal Transport and Neurotransmission

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In the cortex, fast axonal transport is fueled by glycolytic enzymes on-board of axonal vesicles. LDHA recycles NADH into NAD+, producing lactate from pyruvate. The transporter of lactate – MCT1– is also present on their membrane, and uptakes lactate into the vesicles to be released at the synapse. At the synapse, this vesicular lactate might influence neurotransmission via its receptor called HCAR1. In this project, we will investigate HCAR1 subcellular localization in a reconstituted cortico-striatal network in vitro using microfluidic devices.

To have a better understanding of how vesicular lactate influences neurotransmission, we used chemical and genetic approaches to modify MCT1 expression on axonal vesicles. Using a fluorescent glutamate sensor called iGluSnFR, we demonstrated that glutamate release decreases upon vesicular MCT1 inhibition in microfluidic devices. Moreover, using statistical object distance analysis (SODA), and synaptosome extraction approaches, we have observed that HCAR1 is mostly presynaptic in the cortico-striatal network in vitro and in vivo. We are now trying to genetically and chemically regulate HCAR1 levels at the synapse to decipher its mechanisms of action in this precise network of the brain.

Poster 14 : GluCEST as a Translational Biomarker of Synaptic Dysfunction in Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disease whose onset likely involves subtle synaptic dysfunction. Emerging evidence points to glutamatergic synapse impairment as one of the initial pathological events of AD (2), even before the onset of clinical symptoms (3). Synaptic function is strongly coupled to energy metabolism (4). Given the limitations of current diagnostic methods in capturing early disease changes, there is a need for non-invasive biomarkers capable of detecting early-stage alterations. Glutamateweighted chemical exchange saturation transfer (gluCEST) MRI is a novel non-invasive imaging modality that enables high-resolution mapping of glutamate concentrations in the brain (5) and represents a promising tool to assess synaptic integrity in vivo and its link to energy metabolism.

This project aims to explore the potential of gluCEST MRI as a translational biomarker of synaptic dysfunction, using a rat model of the amyloidogenic aspect of AD (McGill-R-Thy1APP transgenic rat model). The model exhibits key aspects of human AD pathology, including intraneuronal amyloid-beta accumulation followed by amyloid-plaque formation, and synaptic deficits (6, 7). The overarching goal is to evaluate gluCEST's capability to detect early synaptic dysfunction and its correlation with biochemical markers, and thereby facilitate subsequent developments of gluCEST MRI for human subjects.

GluCEST imaging will be performed at multiple pathological stages using a 7 Tesla MRI system. The resulting measurements will be validated against ground-truth data derived from immunohistochemistry to quantify synapse density, amyloid and tau pathology, as well as matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) to quantify regional glutamate concentrations (8) as well as other analytes.

Preliminary results show a visible difference in gluCEST signal between grey and white matter.

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