

Imaging Altered Oxidative Metabolism In The Brain Of A Tauopathy Model Using Hyperpolarized ^{13}C MR Spectroscopy

Nicholas Vidas-Guscic¹, Cassandra Leo¹, Madison Heady¹, Ashley Shaw¹, Cornelius Von Morze¹, Jason Ulrich², Aisling Chaney¹, Caroline Guglielmetti¹

¹ Department of Radiology, Washington University School of Medicine, St Louis, MO, United States, ² Department of Neurology, Washington University School of Medicine, St Louis, MO, United States

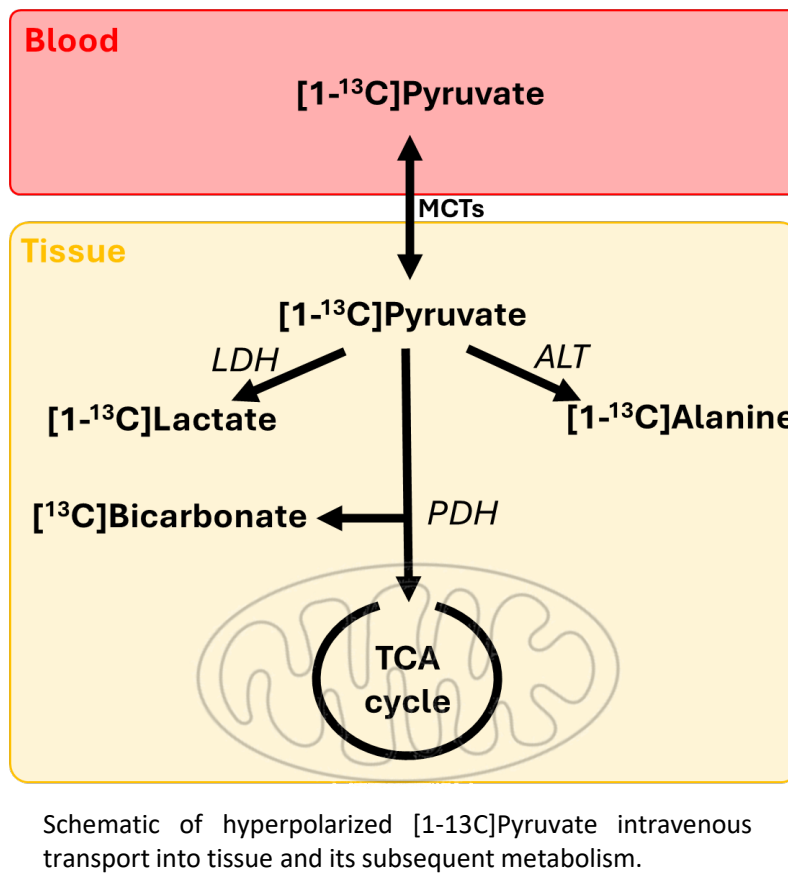
Introduction

Alzheimer's disease (AD) is characterized by altered cerebral glucose metabolism and mitochondrial respiration¹⁻⁵, but how these alterations lead to the neurodegeneration observed in AD is not yet fully understood.

Hyperpolarized (HP) ^{13}C MR spectroscopy (MRS) has emerged as a powerful method to detect *in vivo* metabolic fluxes in real time³. HP ^{13}C MRS provides key information on the fate of pyruvate, the end product of glycolysis, by measuring the conversion of HP [1- ^{13}C]pyruvate (Pyr) to [1- ^{13}C]lactate (Lac) and [^{13}C]bicarbonate (Bic), to investigate changes in glycolytic and oxidative (mitochondria) metabolism, respectively⁴.

Objective

Here, we used MRS of HP [1- ^{13}C]pyruvate to investigate glycolytic and oxidative metabolism alterations in the novel and clinically relevant TE4 model of tau-dependent neurodegeneration⁶.

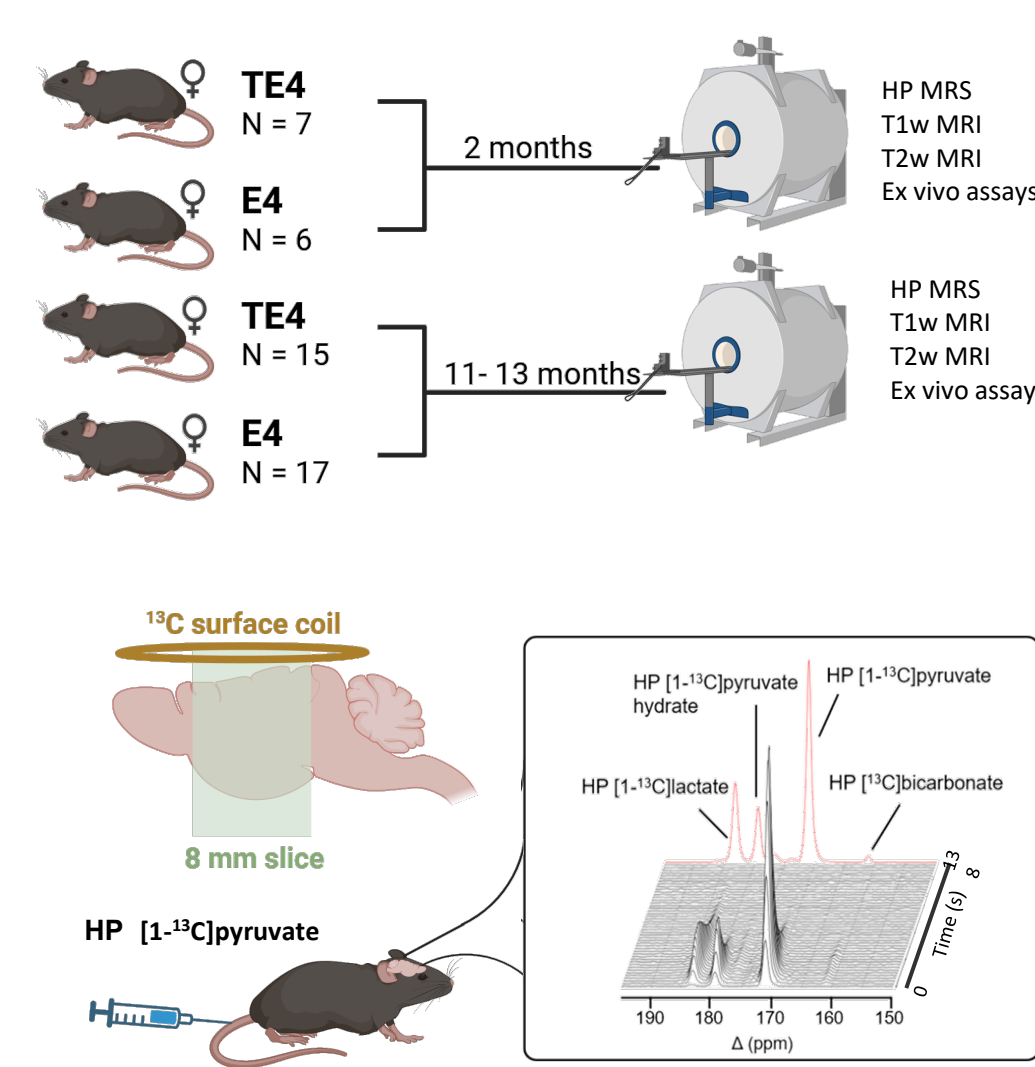


Materials and Methods

Animals: Four groups of mice were used: the tauopathy mouse model (TE4) expressing tau (P301S) and human-*APOE4* at 2 Months (M) (asymptomatic, n=7) and 12M ($\pm$ 1M) (advanced pathology, n=15) and mice expressing human-*APOE4* (E4) at 2M (n=6) and 12M ($\pm$ 1M) (n=17). **Magnetic resonance spectroscopy and imaging:** [1- ^{13}C]pyruvate was polarized in a SPINlab polarizer (GE). Slab dynamic ^{13}C data were acquired using a spectral-spatial pulse sequence from the beginning of the intravenous (i.v.) injection of HP [1- ^{13}C]pyruvate (80 mM) on a 3T MRI scanner (MRSolutions). T_2w and T_1w (pre and post intravenous Dotarem (gadolinium-based contrast agent) injection) MRI was acquired using a 9.4T MRI scanner (Bruker). T_1 ratio maps were calculated as ((Pre-Post)/Pre) i.v. injection).

Colorimetric glutamate assay: Pyruvate dehydrogenase (PDH) and lactate dehydrogenase (LDH) enzyme activities were quantified according to kit protocol.

Statistics: Statistical significance was evaluated using unpaired t-tests comparing E4 and TE4 mice at 2M and 12M (*p<0.05, ** p<0.01, ***p<0.001, ****p<0.0001).



HP ^{13}C MRS detects lower Bic production in the TE4 mouse model

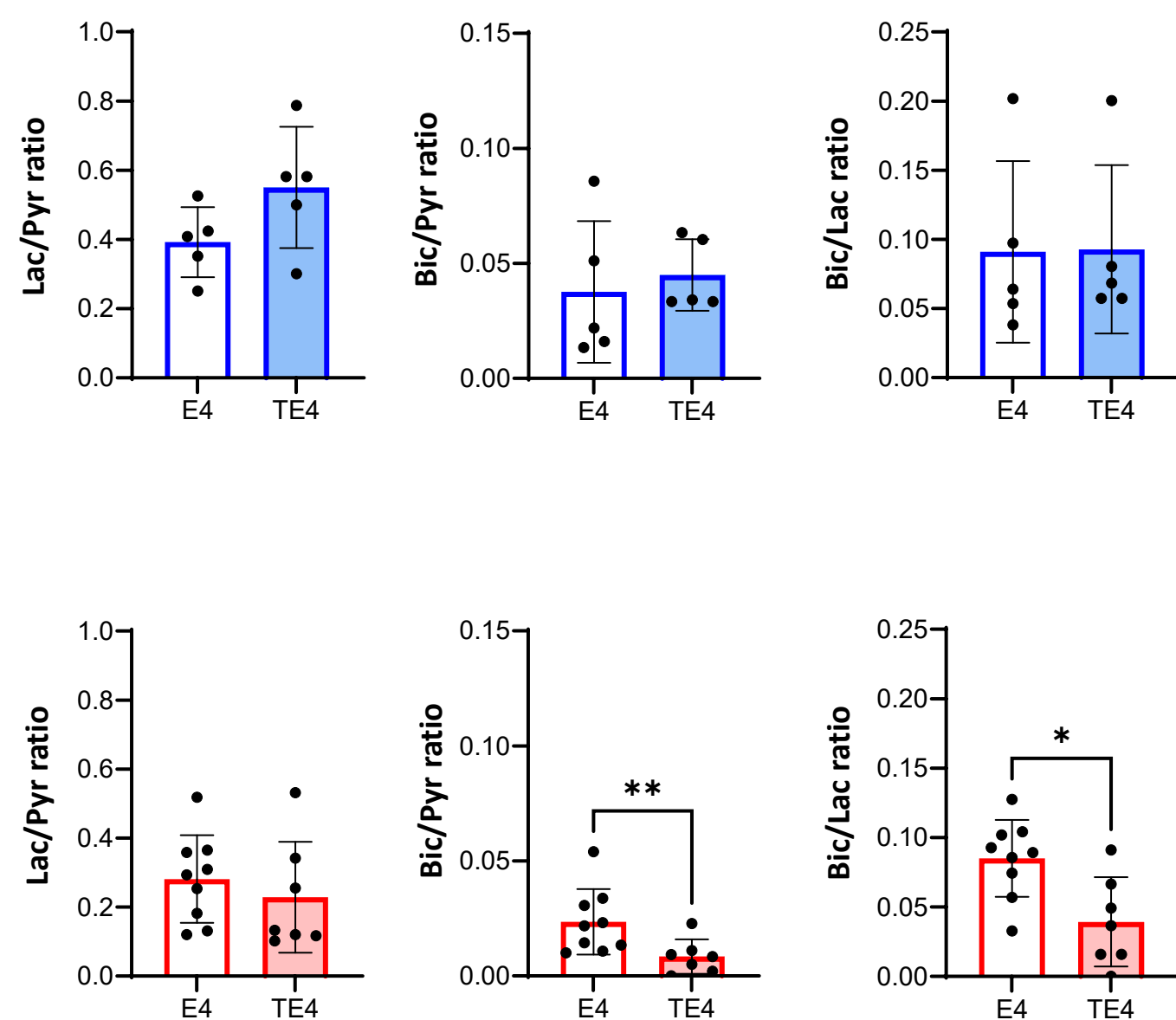
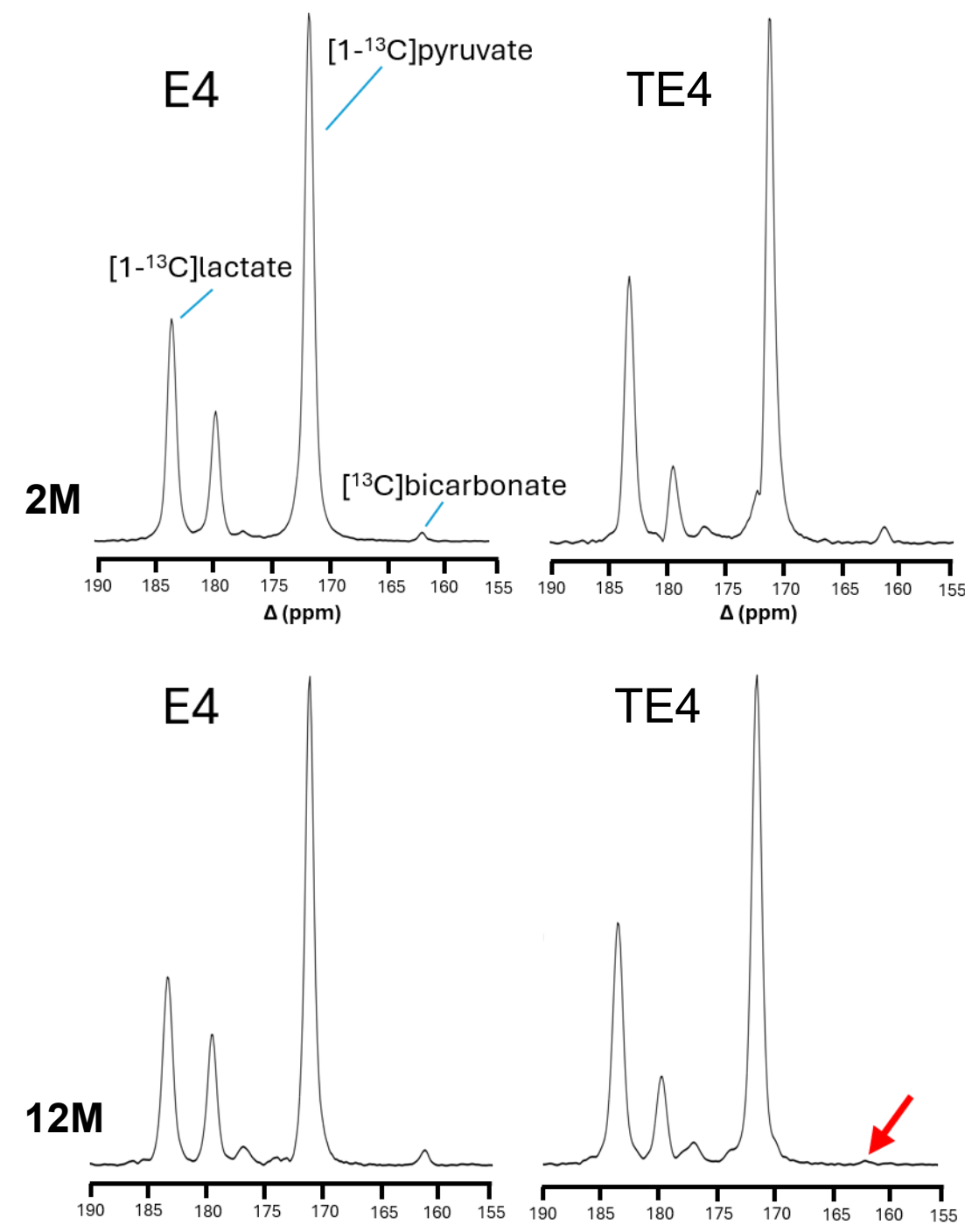


Figure 1: Representative images showing summed hyperpolarized ^{13}C MRS spectra for 2M (top row) and 12M old E4 and TE4 mice. Spectra show resonances for [1- ^{13}C]lactate (183 ppm), [1- ^{13}C]pyruvate (171 ppm), and [^{13}C]bicarbonate (161 ppm). Red arrow highlights smaller Bic peak. Graphs show ratios of Lac/Pyr, Bic/Pyr, and Bic/Lac for 2M (blue graphs) and 12M (red graphs) old E4 (empty bars) and TE4 (filled bars) mice. Mean $\pm$ SD, unpaired t-test, * p < 0.05, ** p < 0.01.

12M old TE4 AD mice produce significantly lower bicarbonate (Bic/Pyr and Bic/Lac), indicative of oxidative metabolism impairment

PDH enzymatic activity is lower in the cortex of TE4 mice

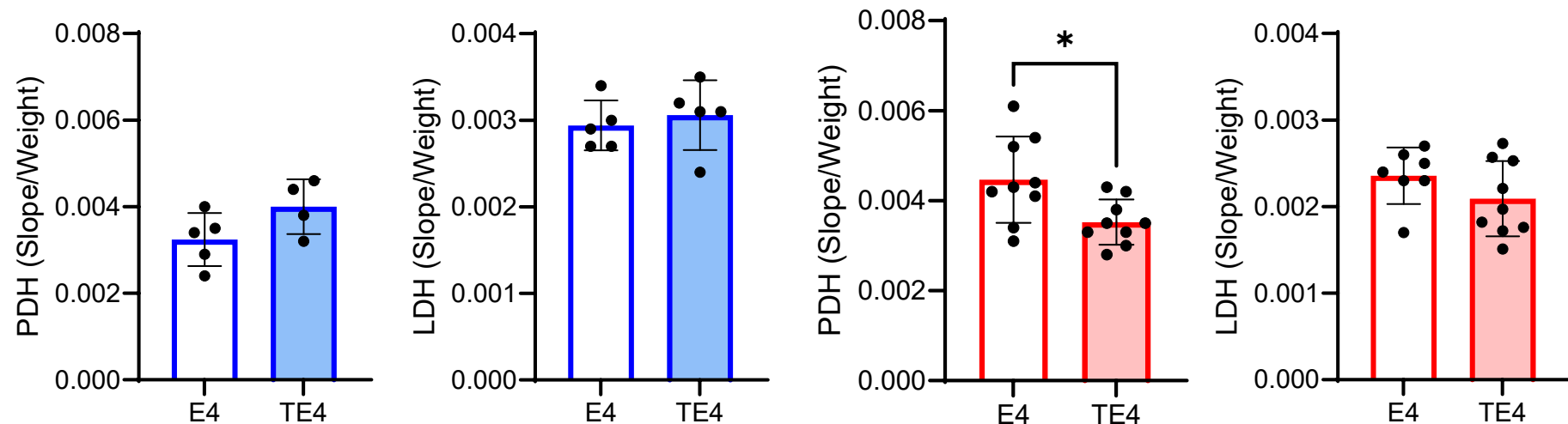
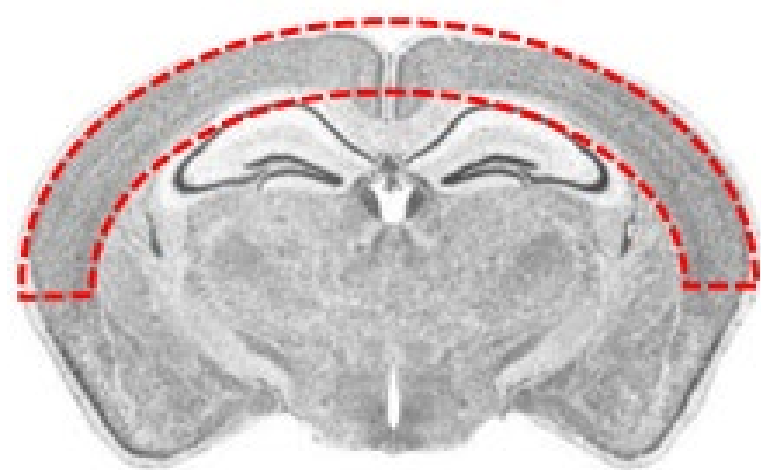


Figure 2: Representative atlas image shows cortical tissue (indicated by red dashed line) collected for enzymatic activity assays. Graphs show enzyme activities corrected for assayed tissue weight for pyruvate dehydrogenase (PDH) and lactate dehydrogenase (LDH) for 2M (blue graphs) and 12M (red graphs) old E4 (empty bars) and TE4 (filled bars) mice. Mean $\pm$ SD, unpaired t-test, * p < 0.05.

At advanced pathological stage, PDH enzymatic is significantly lower in TE4 mice compared to E4 control mice

T_2w MRI reveals severe neurodegeneration in TE4 mice

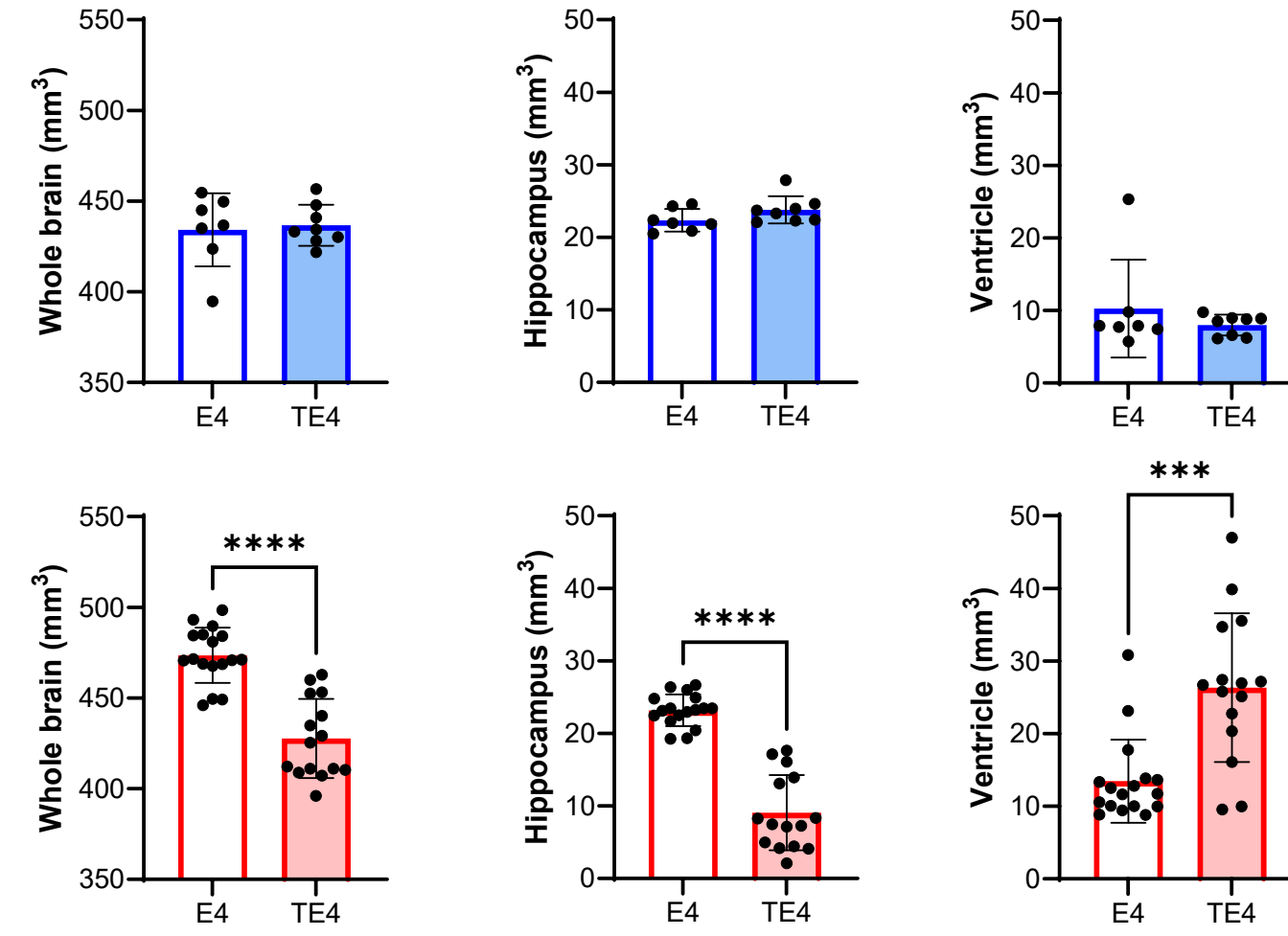
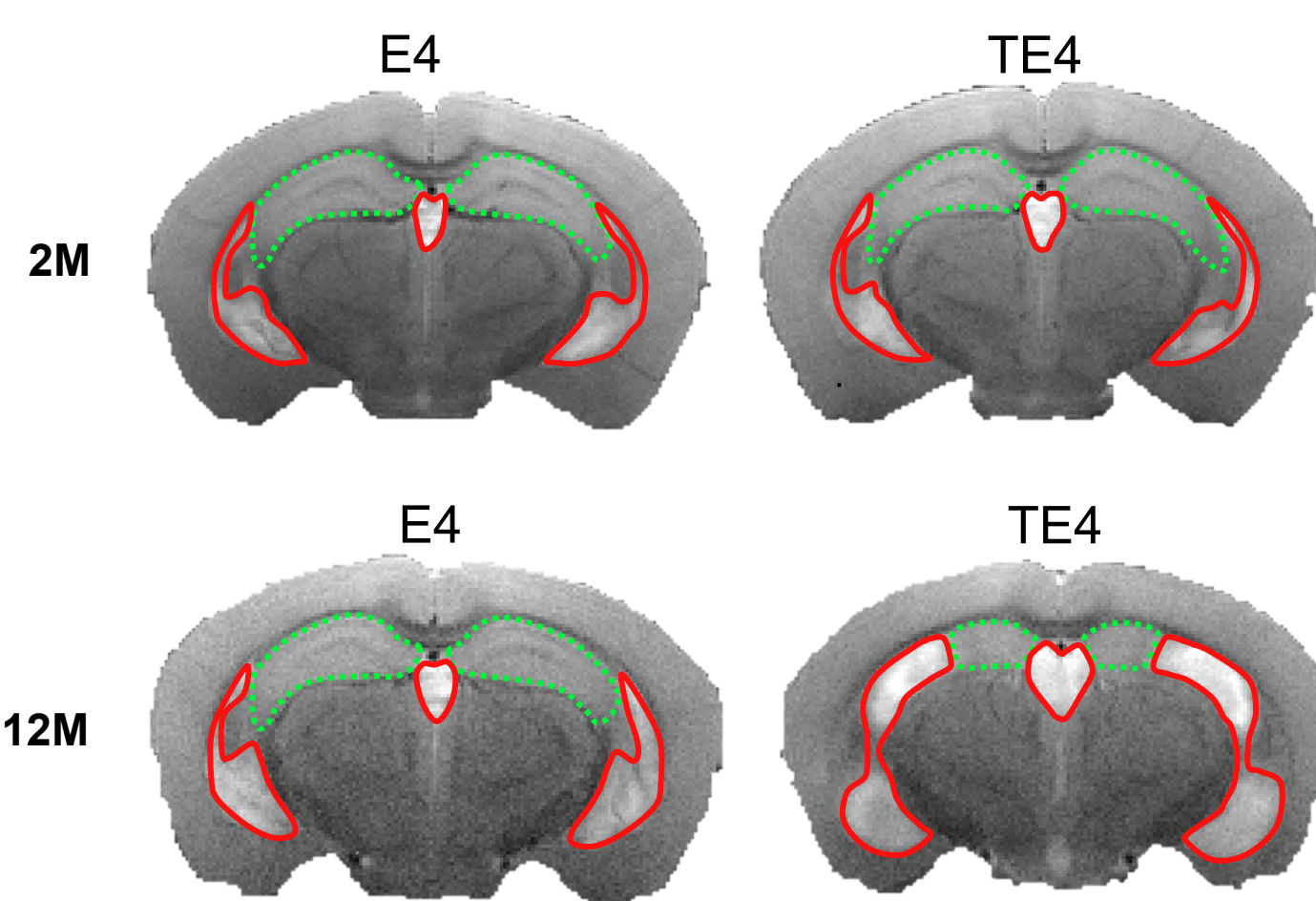


Figure 3: Representative T_2w images of 2M (top row) and 12M old E4 and TE4 mice. Hippocampus (green dashed lines) and ventricles (red solid lines) are highlighted. Graphs show the volume (mm^3) of the whole brain, hippocampus, and ventricles for 2M (blue graphs) and 12M (red graphs) old E4 (empty bars) and TE4 (filled bars) mice. Mean $\pm$ SD, unpaired t-test, *** p < 0.001, **** p < 0.0001.

T_2w MRI reveals severe atrophy of hippocampus and ventricular enlargement. Overall, whole brain volume was significantly lower in 12M old TE4 mice compared to E4 control mice

Contrast-enhanced T_1w MRI shows altered blood brain barrier in TE4 mice

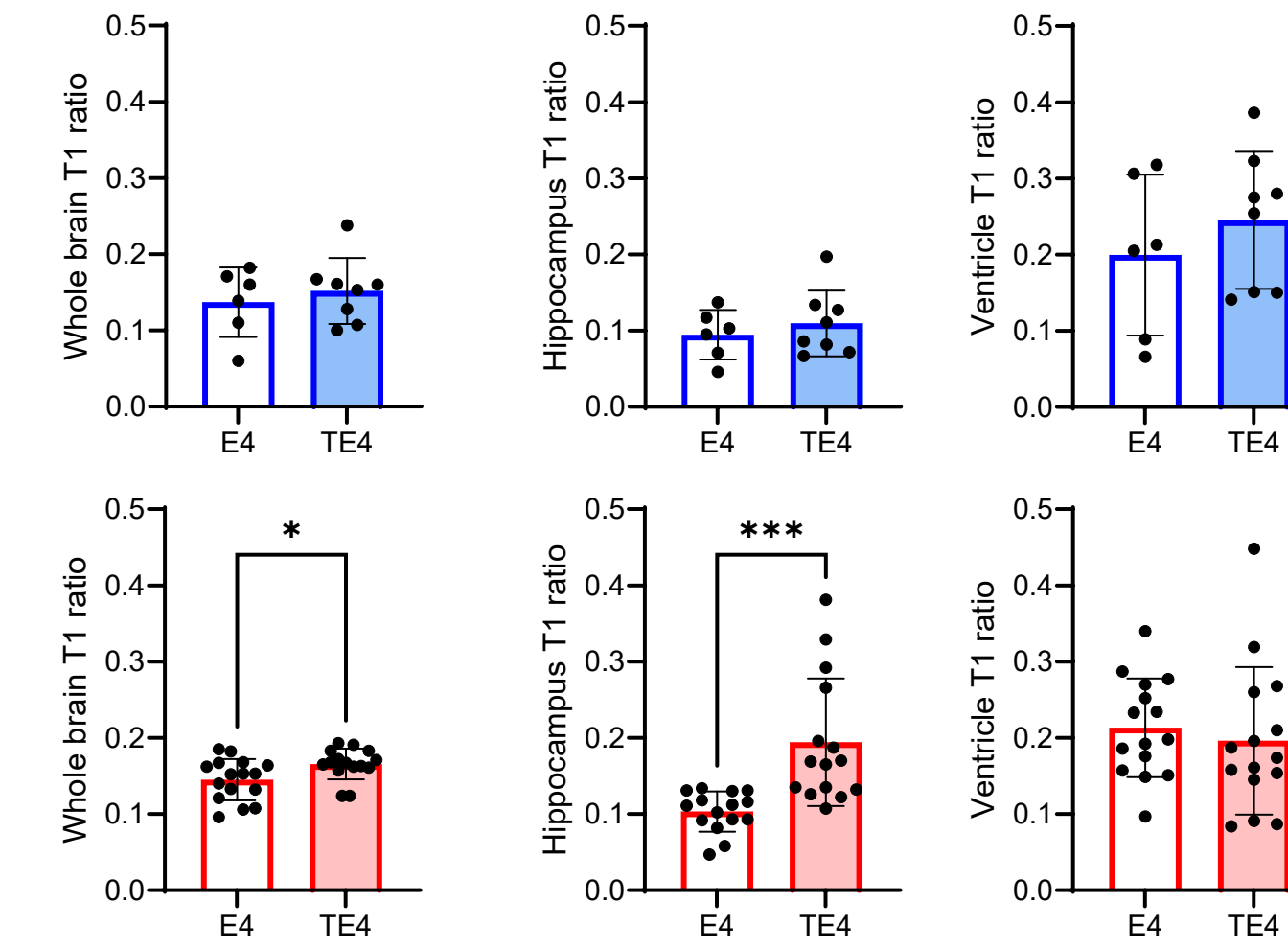
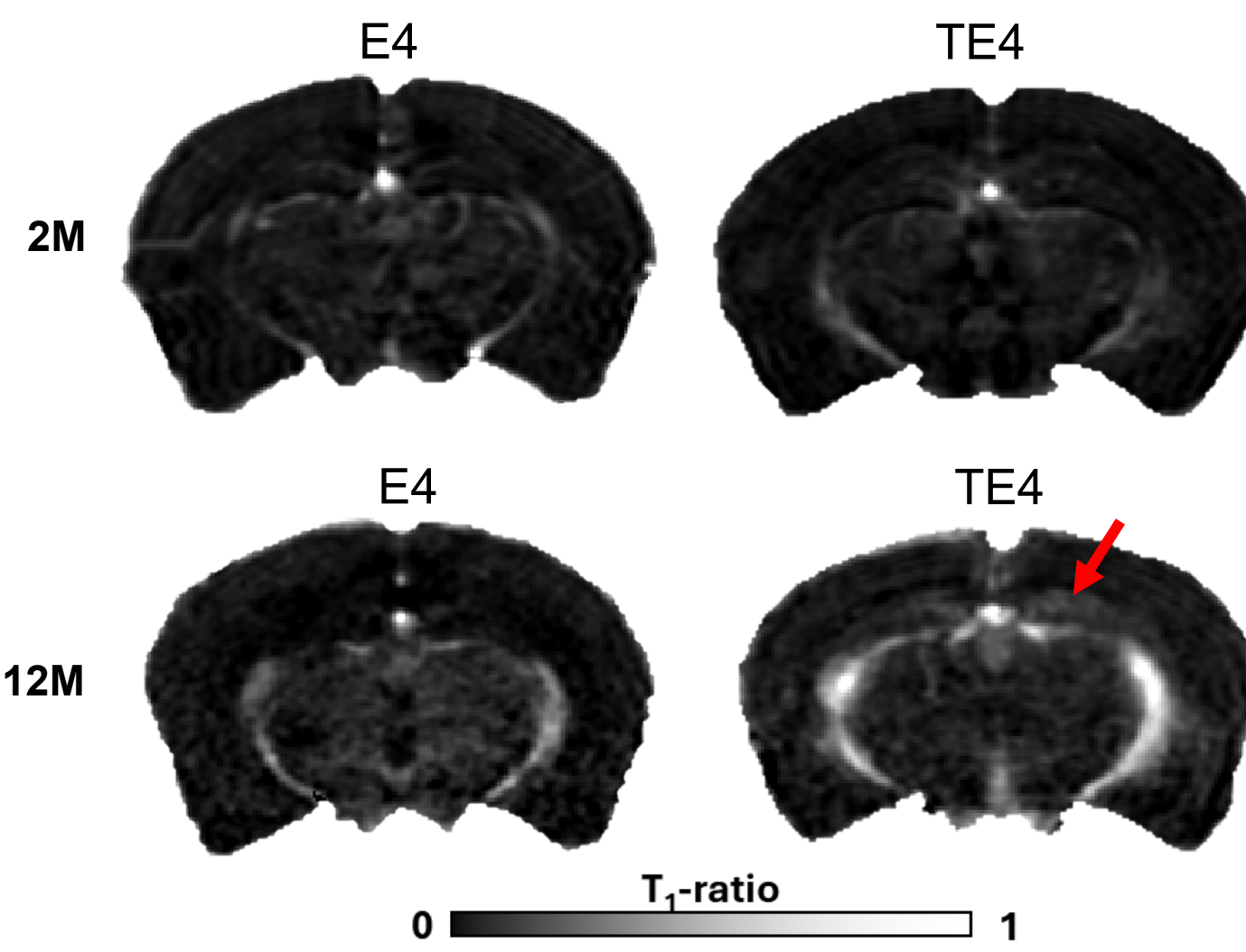


Figure 4: Representative T_1 ratio images of 2M (top row) and 12M old E4 and TE4 mice. Voxel gray scale corresponds to the T_1 -ratio scale below. Graphs show the T_1 ratio from the whole brain, hippocampus, and ventricles regions of interest for 2M (blue graphs) and 12M (red graphs) old E4 (empty bars) and TE4 (filled bars) mice. Mean $\pm$ SD, unpaired t-test, * p < 0.05, *** p < 0.001.

T_1 ratios are higher in the whole brain and the hippocampus, but not the ventricles in 12M old TE4 mice compared to 12M old E4 mice

Discussion

- This is the first report of HP ^{13}C MRS in a clinically relevant tauopathy AD model, revealing brain oxidative (mitochondria) metabolism impairment. This aligns with changes observed in AD¹
- The reduced Bic production is explained by reduced PDH enzyme activity in 12M TE4 mice
- T_2w and T_1w MRI reveal the first *in vivo* assessments of structural impairment in the TE4 mouse model
- These differences are driven by tau pathology and *APOE4* expression as no hyperpolarized MRS or structural MRI differences were observed before pathology onset

References:

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Conclusions

- We conclude that hyperpolarized ^{13}C MRS can detect lower Bic production in the TE4 mouse model at an advanced pathology stage
- These results reveal tau and *APOE4* driven brain oxidative metabolism impairment, which is explained by lower PDH enzymatic activity and align with changes observed in people with AD¹
- Altogether, hyperpolarized ^{13}C MRS may provide a new non-invasive way to study mitochondrial alterations during AD pathogenesis and aid develop and evaluate new treatment in AD

Contact us!
carolineguglielmetti@wustl.edu