Title: Investigating Human Brain Metabolism using Hyperpolarized [2-^{13}C]Pyruvate

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Intro: Methods for the preparation of sterile hyperpolarized (HP) [2-^{13}C]pyruvate imaging studies were developed with spectra demonstrating a feasibility and early investigation into human cerebral energy metabolism using this new modality. Prior animal studies using HP pyruvate with the ^{13}C isotope enriched in the 2-position ([2-^{13}C]pyruvate) have successfully shown direct detection of downstream TCA cycle metabolites as the HP ^{13}C labeled atoms are carried over into acetyl-CoA and then on to [5-^{13}C]glutamate, acetyl-carnitine and other metabolites with known fast conversions. Hence HP [2-^{13}C]pyruvate can provide novel metabolic information from HP [1-^{13}C]pyruvate due to its unique positioning atop multiple anaplerotic and cataplerotic metabolic cascades in the TCA cycle. For this study, dynamic conversions of HP [2-^{13}C]pyruvate to [2-^{13}C]lactate and [5-^{13}C]glutamate were measured aiming to differentiate and quantify metabolism across human brain tissue.

Methods: An imaging approach investigating HP [2-^{13}C]pyruvate metabolism was developed. Using a specialized ^{13}C 32-channel head coil and echo planar imaging sequence, an excitation pulse was designed robustly focusing on improving the resolution of metabolites with known chemical shifts. In this study HP [2-^{13}C]pyruvate, [2-^{13}C]lactate and [5-^{13}C]glutamate were the primary focus for accurate quantification.

Single timepoint data was selected for analysis based on SNR and determined with an appropriate time window to compare initial kinetic modeling results. Calculations for the apparent conversion of pyruvate to lactate (k_{PL}) were performed using an inputless, least-squares model, similar to studies using HP [1-^{13}C]pyruvate (analytical methods available from the Hyperpolarized MRI Toolbox via the Hyperpolarized Technology Resource Center: https://doi.org/10.5281/zenodo.1198915). k_{PG} was quantified with SNR and AUC ratios, and further kinetic behaviors were estimated using connectomic metrics.

Results: Metabolite kinetics, signal-to-noise (SNR) and area-under-curve (AUC) ratios, as well as [2-^{13}C]pyruvate to [2-^{13}C]lactate were measured and showed similar but not identical inter-subject values. k_{PL} calculations were equivalent with prior human HP [1-^{13}C]pyruvate measurements. Comparable results across previously processed [1-^{13}C]pyruvate datasets and newly acquired [2-^{13}C]pyruvate datasets lent verification to the consistency of the inputless model approach. k_{PG} values were calculated and compared across individuals.

Conclusion: Human brain TCA cycle metabolism was investigated using HP [2-^{13}C]pyruvate metabolic imaging. Future studies will aim to investigate centrality metrics processing higher-order descriptors of multi-valued kinetics with advances in machine learning, aiming to elucidate new methods for detecting early stages of neurological disorders. HP metabolic information may also be linked with functional and diffusion MRI modalities to build increasingly comprehensive representations of neural function and structure.

Highlights:

- Human brain TCA cycle metabolism was investigated with HP [2-^{13}C]pyruvate metabolic imaging.
- Similar but not identical glutamate and lactate levels were recorded.
- Kinetic rates for the conversion of pyruvate to lactate (k_{PL}) and pyruvate to glutamate (k_{PG}) were calculated. k_{PL} values agreed with prior [1-^{13}C]pyruvate data.
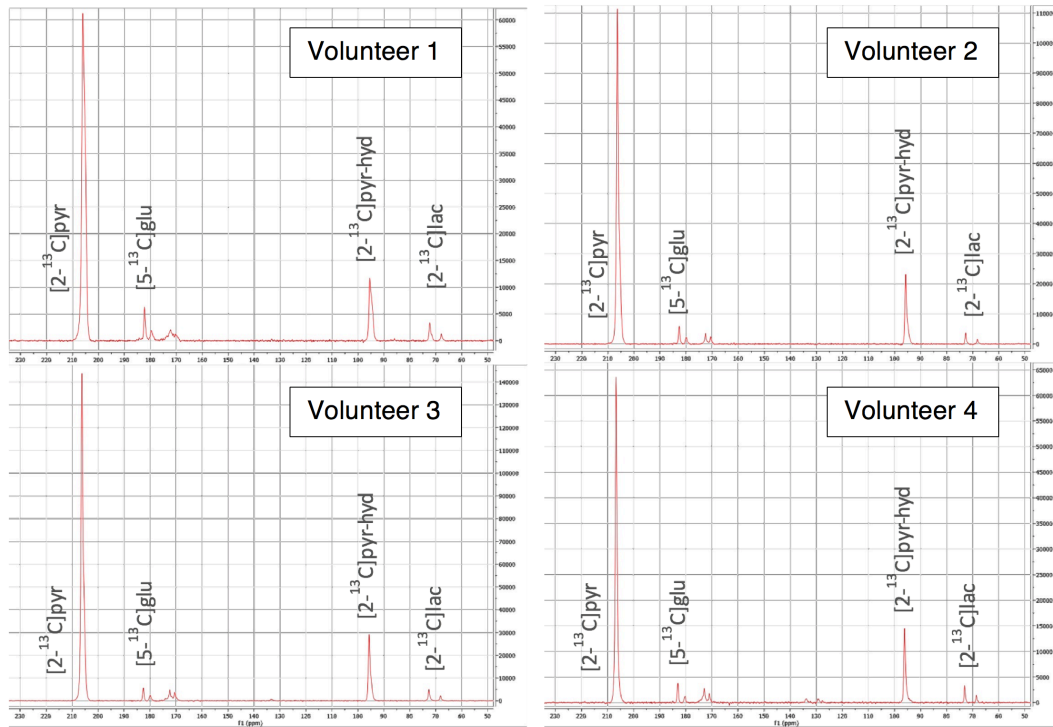
Figures:

Figure 1: Spectra for several volunteers at a single timepoint 16 seconds post-injection. Similar levels of glutamate and lactate reflect the natural underlying biochemistry of a healthy human brain with much higher lactate dehydrogenase (PDH) flux.
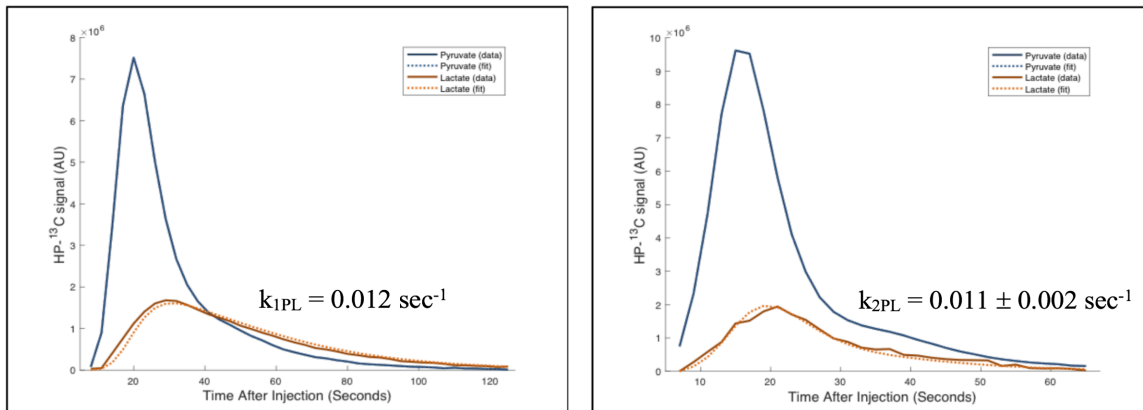

Figure 2: Plots showing similar k_{PL} values across previously acquired [1-^{13}C]pyruvate volunteer datasets and [2-^{13}C]pyruvate volunteer datasets with mean + standard error.