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TITLE: Measuring Glial Metabolism in Repetitive Brain Trauma & Alzheimer's Disease

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CONTRACTING ORGANIZATION: Brigham and Women's Hospital

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The overall aim of the study is to better understand glial metabolism within the context of repetitive brain impacts and Alzheimer's disease and its potential findings in veterans. In preparation for the start of the study, we have conducted a number of studies to quantify the improvement moving from 3T to 7T. We also present data comparing military and sports-related repetitive brain trauma and show that changes in glutamate show similar patterns. These results support our initial hypothesis and illustrate the importance of measuring glial metabolism using indirect detection of 13C-labeled metabolism.

15. SUBJECT TERMS
Repetitive brain trauma, glial metabolism, glutamate, multinuclear spectroscopy, chronic traumatic encephalopathy, Alzheimer's disease, 13C acetate

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1. INTRODUCTION:

Glutamate is a key compound in cellular metabolism with its most important role as a neurotransmitter with which the brain utilizes 80% of energy consumption to maintain this important cycle. Elevated levels of glutamate have been shown to be predictive of outcome in severe traumatic brain injury and our preliminary data from existing studies, have shown that glutamate remains elevated in the chronic stages of repetitive brain trauma (RBT) as well. Current methods of measure brain glutamate using spectroscopy is not specific to different cell types or the dynamic changes that undergo metabolism. We have developed a novel, non-invasive, quantitative method of measuring the dynamic rates of glutamate using ^{13}C-labeled acetate, the primary fuel for glial cells, which can be tracked through the cerebral glutamate synthesis cycle using magnetic resonance spectroscopy. Our goal is to utilize infusion of ^{13}C-labeled acetate in our existing cohort of retired NFL athletes with and without increased glutamate, subjects with Alzheimer's disease (AD), military veterans with a history of traumatic brain injury, and age-matched controls to measure the effect of repetitive brain trauma upon glutamate metabolism. Our hypothesis is that increased glutamate found in these players, will be reflected in up-regulation of glial pathways. The result of the study would be to identify the dysfunctional pathways that underlie glutamate excitotoxicity in sports-related brain trauma. These dysfunctions will provide precise targets for existing glutamate medications that are known to modulate specific pathways. Therefore we anticipate not only providing a better understanding of the metabolic mechanisms of sports-related head injury but also to provide data that will be useful for the development of much needed treatments for this devastating disease.

2. KEYWORDS:

Repetitive brain trauma, glial metabolism, glutamate, multinuclear spectroscopy, chronic traumatic encephalopathy, sports-related brain injury, military-related brain injury, Alzheimer's disease, ^{13}C acetate

3. ACCOMPLISHMENTS:

3.1. Major Goals

Our overall aim will be to better understand glial metabolism within the context of RBT and AD and its potential findings in veterans. Specifically, we will:

Aim 1: Determine the mechanism (excitoxicity?) that results in increased cerebral glutamate and glutamine (Glx) levels by comparing glial metabolic rates in NFL athletes with the highest levels of Glx and those with the lowest levels.

Aim 2: Determine the mechanism (neurodegeneration?) that results in decreased cerebral Glx levels by comparing glial metabolic rates in NFL athletes with the lowest levels of Glx and AD patients.

Aim 3: Identify the specific metabolic pathway that results in alternations of cerebral Glx levels in military and healthy controls as well as in comparison with NFL and AD subjects.

Aim 4: Correlate the glial and glutamate metabolic rates with additional measures obtained in the parent studies including of a) serum, CSF, and genetic biomarkers in the NFL subjects and b) neurocognitive

measures in all cohorts. The result of the study would be to identify the underlying physiological changes in glial metabolism in RBT such as neuroinflammation and glutamate excitotoxicity thus providing targets for much needed treatments as well as provide a safe, non-radioactive test to monitor these treatments.

3.2. Goal Accomplishments

Due to the lengthy delay in obtaining IRB approval, a stop order was put into effect upon October 8th, 2018 after our scientific officer, Dr. Stephen Grate. During this time the only efforts focused upon obtaining IRB approval. IRB approval was obtained on October 11, 2019.

3.3. Training and Professional Development

Due to the stop payment, there were no training and professional development.

3.4. Results Dissemination

Due to the stop payment, studies were halted and results were not disseminated.

3.5. Next Reporting Period Plan

We look forward to reporting progress after the study resumes.

4. IMPACT:

4.1. Principle Discipline

Indirect detection of 13C-acetate using 7T proton spectroscopy has not been utilized before in other studies and therefore will provide highly novel and impactful results. As more and more sites move to higher field strengths, there has not been major developments in our field aside from the improved resolution of images. This method takes advantage of several innovative improvements and could potentially provide a new area of data acquisition that has not been fully explored. We are convinced that publications from this study will be eminently publishable in high impact journals given its technical novelty and important clinical implications.

4.2. Other Disciplines

While the technical improvements impact the radiological fields, the availability of a method to assess glial metabolism, specifically that of glutamate, will provide a non-invasive insight that will not only advance our understanding of glial changes in repetitive brain trauma and neurodegenerative diseases but will also provide potential targets for treatments for in this field that can impact disciplines of pharmaceutical research and ultimately for clinical treatment of long-term impacts of repetitive head trauma.

4.3. Technology Transfer

The availability of the dynamic MRS post-processing algorithms described in this and previous progress reports will be open to the public through open-source software will allow for the ready transfer of the technology developed in this study to the scientific community. All too often the scientific community has difficulty in reproducing methods that are developed “in-house” as the details are often not available. With an open-source approach, much like the aim for FITBIR, these methods will be available for the whole of the scientific community and could provide potential benefits both in our field and other disciplines.

Society

The publication of these novel MRS methods will provide advances in the field of research that can potentially impact society through improved diagnosis and detection of disease.

5. CHANGES/PROBLEMS:

5.1. Changes in approach

There have been no changes to the approach aside from the changes reported in the Year 3 annual report.

5.2. Actual or anticipated problems

Due to the IRB, work has been halted.

5.3. Impact on expenditures

Due to the work halt, there are no expenditures.

5.4. Significant changes in use or care of human subjects

None.

6. PRODUCTS:

6.1. Publications, conference papers, and presentations

Rowland BC, Sreepada L, Lin AP. A comparison of denoising methods in dynamic MRS using pseudo-synthetic data. Magn Reson Med (submitted).

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	Alexander Lin
Project Role:	Principal Investigator
Research Identifier:	orcid.org/0000-0001-8236-880X
Nearest Person Month Worked	0
Contribution to Project	Dr. Lin has been addressing the concerns of the IRB in order to obtain approval. Due to the work halt, no person months were spent.

Name:	Huijin 'Vicky' Liao
Project Role:	Study Coordinator
Research Identifier:	https://www.linkedin.com/in/huijun-vicky-liao-3b682451
Nearest Person Month Worked	0
Contribution to Project	Ms. Liao has assisted Dr. Lin with the acquisition of the 7T spectroscopy data and assisted with the submission of the IRB documentation. Due to the work halt, no person months were spent.

Name:	Eduardo Coello
Project Role:	Postdoc

Research Identifier:	n/a
Nearest Person Month Worked	0
Contribution to Project	Dr. Coello has been preparing for the start of the project by developing a 7T basis set specific to our system. Due to the work halt, no person months were worked.

Name:	Robert Stern
Project Role:	Subaward PI
Research Identifier:	orcid.org/0000-0002-5008-077X
Nearest Person Month Worked	0
Contribution to Project	Dr. Stern has assisted with the recruitment process as described above. Due to the work halt, no person months were worked.

Name:	Michael Alosco
Project Role:	Subaward Study Coordinator
Research Identifier:	n/a
Nearest Person Month Worked	0
Contribution to Project	Dr. Alosco has been in contact with both NFL and AD participants through his own work at BU and will assist with recruitment of subjects for this study. Due to the work halt, no person months were worked.

7.1. Change in Personnel

Nothing to Report.

7.2. Other Organizations

Organization Name: Boston University School of Medicine

Location of Organization: Boston, Massachusetts

Partner's contribution to the project:

- Collaboration: Drs. Robert Stern and Michael Alosco are our collaborators and are responsible for recruitment of subjects, acquisition of neuropsych results, and upload of that data into FITBIR.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to Report.

9. APPENDICES:

MHSRS 2018 Poster.