

**CHARACTERIZATION OF NEUROCHEMICAL AND PHYSIOLOGICAL
CHANGES AFTER BRAIN INJURY USING MAGNETIC RESONANCE
SPECTROSCOPY**

A Thesis Presented to
The Academic Faculty

By

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SPECTROSCOPY**

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
CDC	Centers for Disease Control and Prevention
Cho	Choline
Cr	Creatine
CSF	Cerebrospinal fluid
CST	Chemical shift thermometry
DSC	Dice similarity coefficient
FDR	False discovery rate
Glx	Glutamine + glutamate
JVC	Jugular vein compression
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
mTBI	Mild traumatic brain injury
myoI	Myo-inositol
M1	Primary motor cortex
NAA	<i>N</i> -acetylaspartate
NIH	National Institutes of Health
tCho	Total glycerophosphocholine + phosphocholine
tCr	Total creatine + phosphocreatine
tNAA	Total <i>N</i> -acetylaspartate + <i>N</i> -acetylaspartyl glutamate

SUMMARY

Diagnosis and prognosis of brain injury in contact sports, including American football, are challenging. As part of a larger prospective controlled clinical trial, the goal of this thesis was to use magnetic resonance spectroscopy (MRS) to investigate alterations in brain neurochemistry in a cohort of high school athletes over a season of American football as a function of head impact exposure, concussion diagnosis, and application of a jugular vein compression (JVC) collar. Single-voxel MRS data were acquired in 215 male participants in the primary motor cortex (M1) and rostral anterior cingulate cortex (ACC) pre- and post-season. Metabolites of interest included total *N*-acetylaspartate + *N*-acetylaspartyl glutamate (tNAA), total glycerophosphocholine + phosphocholine (tCho), myo-inositol (myoI), and glutamine + glutamate (Glx), all relative to total creatine + phosphocreatine (tCr). Group-wise differences in metabolites were determined using Friedman's or Mann Whitney U tests. Relationships between changes in metabolites/tCr over the season and head impacts with mean *g*-force thresholds between >20 *g* and >150 *g*, in 10 *g* intervals, were analyzed using linear regressions, accounting for effects of concussion and JVC collar.

Key results included a significant decrease in tCho/tCr and increase in Glx/tCr in the ACC, and significant decrease in myoI/tCr in M1 were observed from pre- to post-season. The relationship between changes in tCho/tCr in both M1 and ACC and head impacts with mean *g*-force thresholds between >80 *g* and >140 *g* differed significantly between participants with and without a diagnosed concussion. Post-hoc analyses revealed increased tCho/tCr was positively associated with impacts for thresholds >100 *g* and >110 *g* in M1 in participants with a diagnosed concussion. In the collar group,

changes in myoI/tCr in the ACC were significantly and negatively associated with head impacts with mean *g*-force thresholds of >110, and >120 *g*.

This is the largest longitudinal study to-date examining the relationship between metabolite alterations measured with MRS and head impact exposure in a cohort of high school football athletes. The associations between changes in tCho/tCr and head impacts at high magnitudes in participants with a diagnosed concussion suggest tCho may be a key indicator for concussion-related brain alterations after repeated head impacts in competitive sports.

CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1 Concussion in Sports

Traumatic brain injuries (TBI) are commonly caused by a blunt force that damages the brain tissue and can lead to permanent physiological and psychological impairments in severe cases. Mild TBI (mTBI), commonly known as concussion, occur frequently in contact sports,¹ present with less severe but more heterogeneous symptoms across individuals, and are more challenging to diagnose and prognose. The Centers for Disease Control and Prevention (CDC) estimate ~135,000 athletes with concussion, a form of mTBI, are admitted to emergency departments annually in the United States.² Over the past two decades, increasing numbers of concussions have been observed across high school and collegiate athletes due, in part, to improved reporting and increased participation in sports.^{1,3} Among contact sports, the highest rates of concussion are typically observed in American football.^{2,4-6} During football practices and games, athletes experience head impacts of varying number and magnitude which can lead to neurological impairment. As the diagnosis of concussion is often based on subjective evaluation of athletes' signs and symptoms, the precise effect of head impacts across a range of forces is unclear,⁷⁻⁹ and the heterogeneous nature of the injury and variability in clinical presentation remain key challenges.¹⁰

1.2 Magnetic Resonance Spectroscopy and Brain Metabolite Alterations after Concussion

Non-invasive neuroimaging methods provide an objective way to classify concussion, and prior research in contact sports has reported neurological changes using magnetic resonance imaging (MRI).¹¹⁻¹³ Among these, proton MR spectroscopy (MRS) facilitates quantification of brain metabolite changes.¹⁴⁻¹⁷ Compared to other clinical methods of characterizing metabolic profiles in the brain, MRS is non-invasive and facilitates repeated and quantitative measurements of brain metabolites, with potential applications in assessing injury progression and response to treatment.¹⁶

Previous work using MRS evaluating collegiate American football players with a diagnosed concussion found lower *N*-acetylaspartate (NAA) relative to total creatine (tCr, creatine + phosphocreatine) at both acute (5 days) and chronic (6 months) time points compared to players who did not experience a concussion.¹³ Longitudinal investigations of athletes participating in contact sports reported lower myo-inositol (myoI) at mid- or post-season compared to pre-season.^{17,18} Moreover, in a cohort of high school athletes, a decrease in glutamine + glutamate (Glx) and an increase in glycerophosphocholine + phosphocholine (tCho) relative to tCr was observed mid-season compared to pre-season.¹⁹ These results suggest brain metabolites may be a marker of injury; however, due to differences in acquisition methods and experimental time points, combined with the heterogeneous nature of head injuries, trends in neurochemical changes after concussion remain inconsistent.¹⁴

1.3 Head Impacts and Neurochemistry

As concussion is heterogeneous in its presentation and outcomes, several mechanical parameters including linear and angular acceleration and mechanical stress have been used as metrics for severity of head injuries and are associated with neurological alterations.^{9,19-21} Previous work in a cohort of 24 high school football players reported a positive correlation between mid-season tCho/tCr in the dorsal lateral prefrontal cortex and mean peak translational acceleration for impacts at g-force threshold of >50 g between pre- and mid-season.¹⁹ With much of the prior literature focusing on comparisons between neurochemical differences in athletes playing contact sports (i.e., American football and soccer) and non-contact sports (i.e., track-and-field and swimming), large-scale longitudinal studies of neurochemical alterations in young athletes as a function of head impacts is warranted.^{14,22}

1.4 Jugular Vein Compression Collar

The present MRS study was a part of a large longitudinal controlled trial, in which the efficacy of a jugular vein compression (JVC) collar in mitigating brain changes after head impacts was evaluated with several metrics beside brain metabolites, including diffusion tensor imaging (DTI) metrics and behavioral and cognitive assessment outcomes. Prior findings in this trial indicate a JVC collar reduces microstructural brain changes associated with repetitive head impacts in American football athletes.^{20,23} However, the effect of wearing a JVC collar has not been examined with respect to metabolites and is unknown on brain neurochemistry.

1.5 Study Objectives

The goals of the present study were to quantify changes in brain metabolites between participants with and without a diagnosed concussion as well as between participants with and without the use of a JVC collar, and examine the relationships between brain metabolite changes and mean *g*-force of head impacts (in units of peak linear acceleration) during a single season of American football in a longitudinal cohort of male high school athletes.

CHAPTER 2

MATERIALS AND METHODS

2.1 Subject Characteristics and Study Design

This prospective controlled clinical trial was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board and registered with clinicaltrials.gov (NCT# 04068883). Written informed consent was obtained from participants, or from a parent or guardian if the participant was under the age of 18 years. All participants under 18 years of age provided written assent prior to participation. Male high school football athletes between 13 to 18 years old ($n=215$; mean \pm standard deviation age = 15.9 ± 1.0 years) were recruited from seven greater Cincinnati high schools. MRS was acquired at two timepoints: 1) before the start of the regular season (pre-season) and 2) at the end of the regular season of play (post-season). An additional MRS scan was acquired from participants with a diagnosed concussion and took place approximately one week after the concussive event (post-concussion). All concussions were diagnosed by the medical staff at each school. Exclusion criteria included a lack of medical clearance to play competitive sports, a history of neurological deficits, cerebral infarction or severe head trauma, and contraindications to MRI such as the presence of metal. MRS data was acquired in a total of 223 unique subjects.

2.2 Head Impact Tracking

Exposure to head impacts during the season was monitored using an accelerometer (CSx System Ltd., Auckland, New Zealand), affixed below each participant's left mastoid. The

CSx accelerometer is comprised of a triaxial accelerometer and gyroscope, quantifying linear and rotational accelerations at 2300 Hz and 1000 Hz, respectively. Any impacts exceeding 10 g would trigger recording of the g-force for the next 45 ms, and the peak g-force during this interval was recorded as the magnitude of the impact. To reduce false positive impacts, data were filtered as previously described.²⁰ Specifically, data were removed in the case of three or more consecutive impacts >20 g and <10 s apart within a 30 s time window, as these were largely due to factors unrelated to football such as removal of the accelerometer. Filtering removed 28.5% of the total number of head impacts recorded across all participants. Head impact data, including number of impacts and total g-force, were stratified by g-force thresholds between >20 g to >150 g in 10 g intervals. Mean g-force was calculated as the sum of total g-force divided by the number of impacts at each threshold.

2.3 Jugular Vein Compression Collar

All participants were assigned to one of two groups: JVC neck collar group ('collar', 4 teams, n=139), or a non-collar group ('non-collar', 3 teams, n=145). Participants in the collar group wore a JVC collar (Q-collar, Q30 Innovations) during practices and games throughout the competitive season (from early August to late November depending on the final regular season game for each team). With no reported adverse events in the cohort, the JVC collar, which is placed around the bottom of the neck, compresses the jugular vein lightly, resulting in venous dilation in the brain so the amount of energy absorption by the brain is reduced during a head impact.

2.4 MRI and MRS Acquisition and Analysis

MR data was acquired on three 3 Tesla Philips whole-body MR scanners (Achieva, Ingenia, and Elition). Each participant completed all respective MR examinations on the same scanner. The sequence acquisition parameters were identical across scanners. The sagittal T1-weighted imaging used to position the MRS voxel was acquired with a three-dimensional, gradient recalled echo sequence (repetition time (TR) = 8.1 ms, echo time (TE) = 3.7 ms, inversion time (TI) = 1070 ms, field of view (FOV) = 256 mm x 256 mm, voxel size = 1 mm isotropic, number of slices = 180). Single-voxel MRS data was acquired in the primary motor cortex (M1) and anterior cingulate cortex (ACC) using a point-resolved spectroscopy sequence (PRESS; TR = 2000 ms, TE = 30 ms, averages = 96, complex data points = 1024, voxel size = 2 cm isotropic, bandwidth = 2000 Hz, flip angle = 90°). Both water-suppressed (via 3 chemical shift selective saturation pulses) and non-water-suppressed spectra were acquired. Overlap of voxel placement from pre- to post-season was optimized by performing rigid-body realignment of the pre-season T1-weighted image to the post-season T1-weighted image during the latter scan session and multiplying the pre-season voxel coordinates by the resulting transformation matrix. MR spectra were analyzed using LCModel v6.3-1.²⁴ Metabolites of interest included total NAA (tNAA, NAA + *N*-acetylaspartyl glutamate (NAAG)), tCho, myoI, and Glx, relative to tCr, which served as an internal reference to minimize confounding effects such as scanner differences and repeated acquisition across multiple days. Relative tissue fractions (gray matter, white matter, cerebrospinal fluid (CSF)) of each MRS voxel were calculated using tissue probability maps generated from the Unified Segmentation Algorithm packaged in the Statistical Parametric Mapping toolbox (Wellcome Centre for

Human Neuroimaging, University College London, London UK). Metabolite concentrations were corrected for CSF fraction and T1 and T2 relaxation times of gray and white matter.²⁵ Dice similarity coefficient (DSC) for the pre-season and post-season voxel positions was calculated as two times the overlapped area divided by the total area in both voxels for each subject.²⁶ MR spectra were included if the voxel positions had a DSC >0.5. Metabolites with Cramer-Rao lower bounds greater than 30% were excluded.

2.5 Statistical Analysis

All analysis was performed using MATLAB (v2020b, Mathworks). Metabolite ratios are reported as the median \pm standard error (SE) unless otherwise noted. Significance was determined by $p \leq 0.05$, and false discovery rate (FDR)²⁷ corrected p-values are reported for group-wise comparisons. Data was visually assessed for normality and non-parametric statistical tests were used when distributions were not normal. For participants without a diagnosed concussion, non-parametric Wilcoxon signed-rank tests were used to evaluate the differences in metabolite/tCr for all four metabolites between pre-season and post-season. For participants with a diagnosed concussion, non-parametric Friedman's tests were used to evaluate differences in metabolite/tCr for all four metabolites between pre-season, post-concussion, and post-season. Differences in the changes in metabolite/tCr normalized to the pre-season baseline [$\Delta_{(post-pre)/pre}$ *metabolite/tCr*], where $\Delta_{(post-pre)/pre}$ represents (post-season – pre-season)/pre-season)] for all four metabolites between concussion and JVC collar groups were evaluated with non-parametric Mann-Whitney *U* tests.

Univariate linear regressions were used to assess the relationship between $\Delta_{(post-pre)/pre}$ *metabolite/tCr* (response), mean *g*-force of head impacts (predictor), concussion (0 or 1, covariate) and JVC collar (0 or 1, covariate). The interaction effects of mean *g*-force \times concussion and mean *g*-force \times collar were also assessed to identify changes in relationships as a function of concussion and collar, respectively. If significant interaction effects were observed, post-hoc regressions were performed. To evaluate differences in associations of head impacts acquired prior to and after diagnosed concussion, linear mixed-effects models using $\Delta_{(post-pre)/pre}$ *metabolite/tCr* (response), mean *g*-force of head impacts (fixed effect predictor), pre-concussion or post-concussion (covariate), and subject (random effect for slope and intercept) were used. The Akaike information criterion (AIC) was used for mixed-model selection.

CHAPTER 3

RESULTS

3.1 Study Cohort and MR Spectra

Among 223 subjects who had completed MRS scans, spectra from 215 unique participants were included (210 spectra in M1 and 190 spectra in the ACC) (**Figure 3.1**).

Of the 215 participants, 24 were diagnosed with a single concussion during the season and no participants were diagnosed with more than one concussion. Sample spectra and corresponding T1-weighted images with overlaid voxel positions are shown in **Figure 3.2** for M1 and in **Figure 3.3** for the ACC.

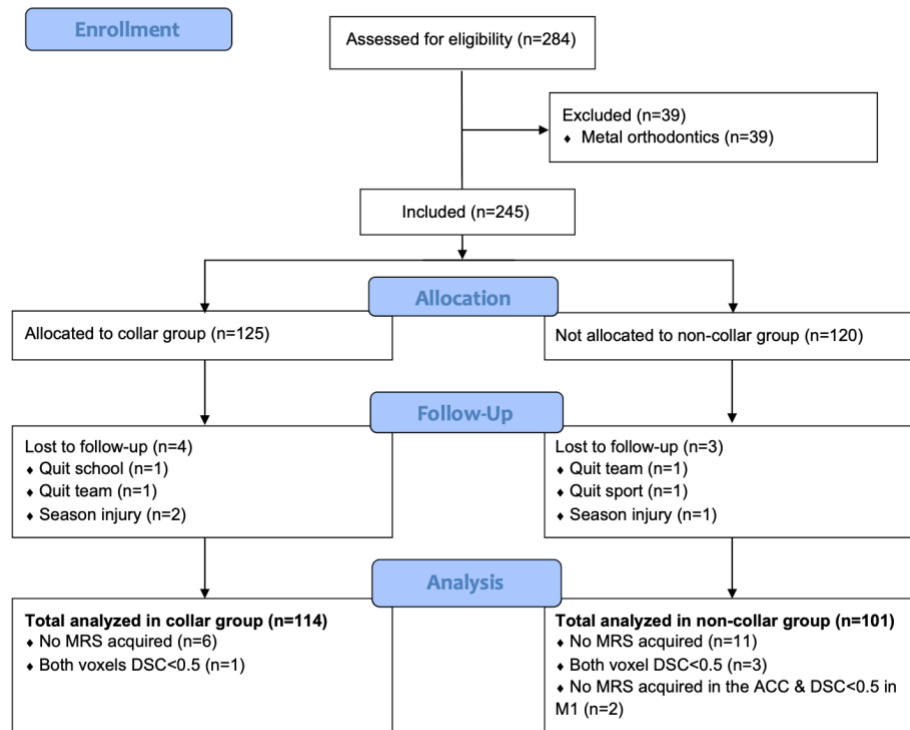


Figure 3.1. CONSORT flow diagram for clinical trial participants.

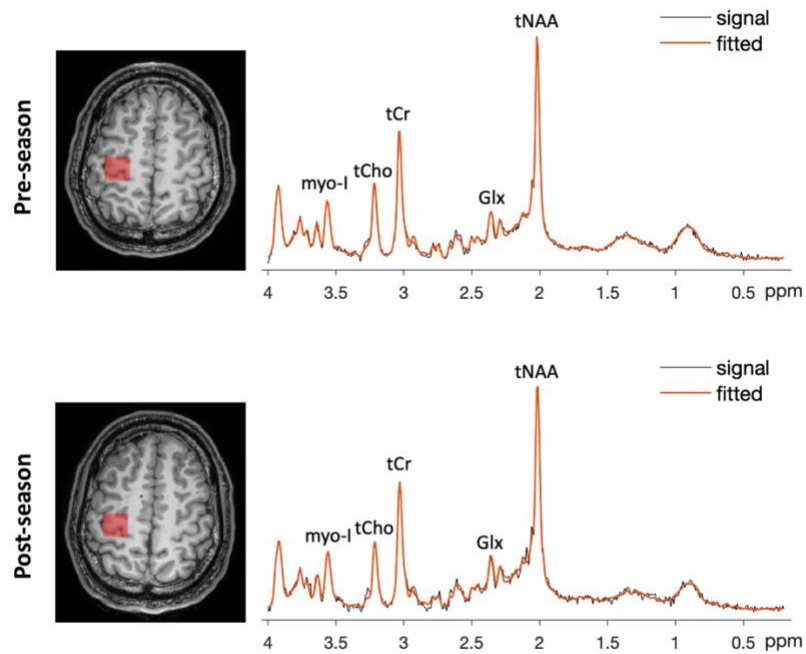


Figure 3.2. Magnetic resonance spectroscopy (MRS) voxel placement in the left primary motor cortex (red box) overlaid onto T1-weighted images, accompanied by corresponding MR spectra. Spectra were fitted using LCModel. Images are shown in radiological orientation. (tNAA = total *N*-acetylaspartate + *N*-acetylaspartyl glutamate; tCho = total glycerophosphocholine + phosphocholine; myoI = myo-inositol; Glx = glutamine + glutamate)

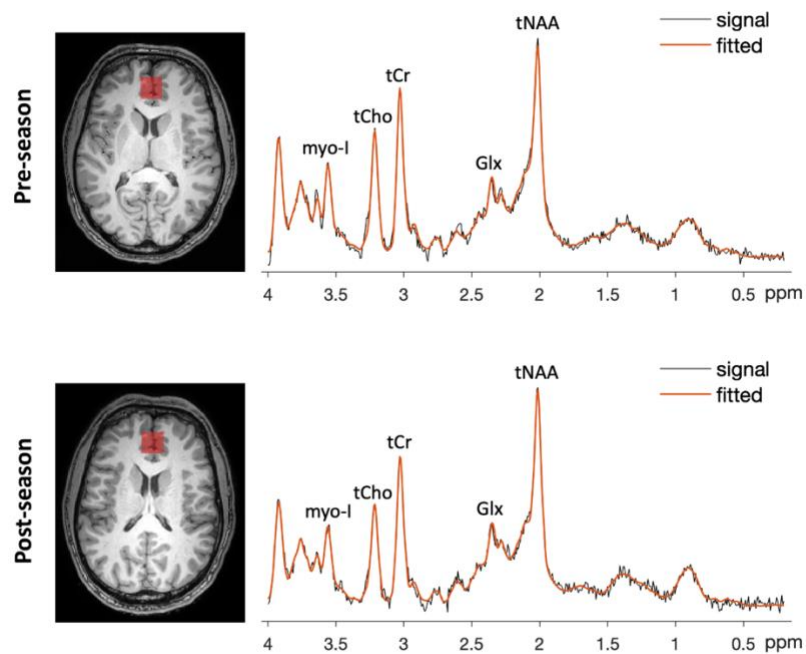


Figure 3.3. Magnetic resonance spectroscopy (MRS) voxel placement in the rostral anterior cingulate cortex (red box) overlaid onto T1-weighted images, accompanied by corresponding MR spectra. Spectra were fitted using LCModel. Images are shown in radiological orientation. (tNAA = total *N*-acetylaspartate + *N*-acetylaspartyl glutamate; tCho = total glycerophosphocholine + phosphocholine; myoI = myo-inositol; Glx = glutamine + glutamate)

3.2 Group-wise Comparisons

In participants without diagnosed concussion, a significant decrease was observed in myoI/tCr in M1 from pre- to post-season but did not survive following FDR correction (**Appendix Table A.1**). In the ACC, a significant decrease of tCho/tCr and an increase of Glx/tCr were observed from pre- to post-season with FDR correction (**Appendix Table A.1**). No significant differences between pre- and post-season for any metabolite/tCr were observed in either M1 or the ACC in participants with a diagnosed concussion (**Appendix Table A.2**). $\Delta_{(post-pre)/pre}$ *metabolite/tCr* for all four metabolites in M1 and the ACC were not significantly different between participants with or without a diagnosed concussion (**Appendix Table A.3**). Similarly, the collar had no significant effect on any $\Delta_{(post-pre)/pre}$ *metabolite/tCr* in M1 or in the ACC (**Appendix Table A.4**). No difference in tCr relative to water was observed between pre- and post-season, supporting the use of tCr as an internal reference for the remaining metabolites.

3.3 Trends in Mean g-force of Head Impacts and Concussion Rates

A histogram of head impacts at a mean g-force threshold of >80 g revealed a relatively normal distribution for mean impacts with no clear trends in median hits (**Figure 3.4**). A histogram of number of impacts at a threshold of >80 g in participants with and without diagnosed concussion showed similar numbers and distributions of impacts (**Figure 3.5**). In participants with diagnosed concussion, the histogram of dates of the concussion shows no clear trends in concussion timing across the season (**Figure 3.6**).

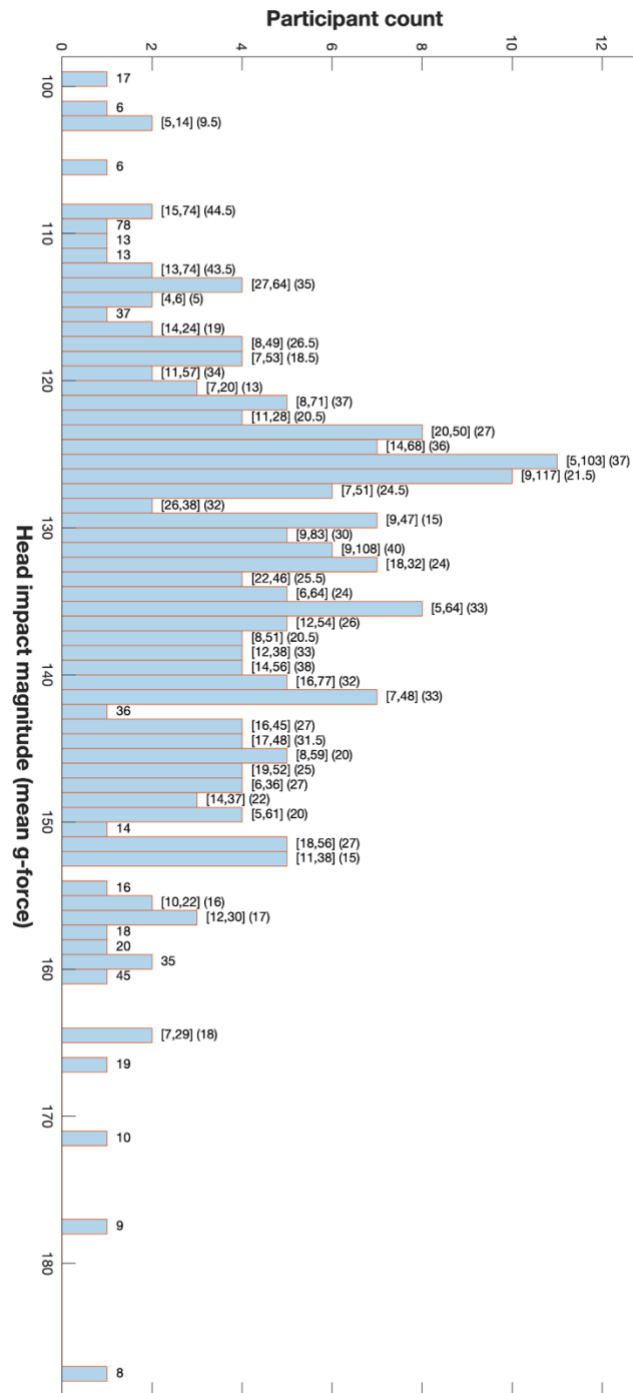


Figure 3.4. Histogram of head impacts at a mean g-force thresholds of >80 g and corresponding number of impacts (range in brackets and median in parentheses) across all subjects.

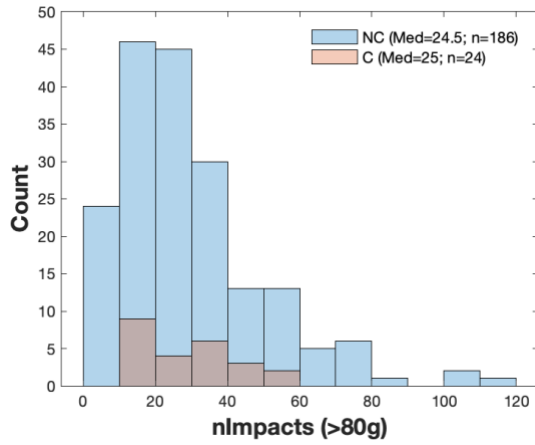


Figure 3.5. Histogram of number of impacts at a g-force threshold of >80 g for participants with (C) and without (NC) a diagnosed concussion.

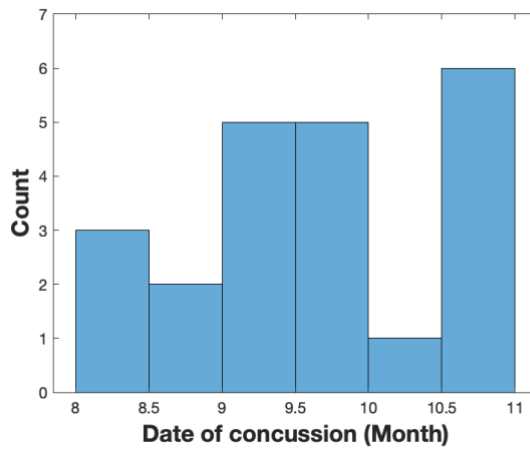


Figure 3.6. Histogram of concussion dates from the beginning of August to the end of October in 2-week intervals. The x-axis refers to month by number (8 = August, 9 = September, 10 = October).

3.4 Relationships Between Metabolite Changes and Mean *g*-force in M1

In M1, the relationship between $\Delta_{(post-pre)/pre} tCho/tCr$ and head impacts varied significantly between participants with and without a diagnosed concussion for mean *g*-force thresholds between >80 *g* and >140 *g*, but not for thresholds below 80 *g* or at >150 *g* (**Figure 3.7A, Appendix Table B.1**). Relationships between $\Delta_{(post-pre)/pre} metabolites/tCr$ in M1 and head impacts did not vary for any metabolite between collar and non-collar groups (**Appendix Table B.1**). Post-hoc regressions revealed significant positive associations between $\Delta_{(post-pre)/pre} tCho/tCr$ in M1 and head impacts with mean *g*-force thresholds of >100 and >110 *g* in participants with a diagnosed concussion (**Appendix Table B.2**). Within the concussion cohort, a significant interaction effect of mean *g*-force \times time of injury was observed for thresholds of >100 and >110 *g*, suggesting the trend between changes in *tCho/tCr* in M1 and head impacts prior to the diagnosed concussion (between pre-season and post-concussion) differed from the trend after the concussion (between post-concussion and post-season) (**Figure 3.8**). Relationships between $\Delta_{(post-pre)/pre} metabolite/tCr$ in tNAA, myoI and Glx in M1 and head impacts with any mean *g*-force thresholds were not significant and did not vary between participants with or without a diagnosed concussion or between collar or non-collar groups (**Appendix Tables B.3-B.5**).

3.5 Relationships Between Metabolite Changes and Mean *g*-force in the ACC

In the ACC, the relationship between $\Delta_{(post-pre)/pre} tCho/tCr$ and head impacts with mean *g*-force thresholds of >80, >100, >110, >120, >130 and >140 *g* was significantly different between participants with and without a diagnosed concussion (**Figure 3.7B,**

Appendix Table B.6). The relationship between $\Delta_{(post-pre)/pre} myoI/tCr$ in the ACC and head impacts with mean *g*-force thresholds of >110, >120, and >130 *g* varied significantly between collar and non-collar groups (**Appendix Table B.7**). Post-hoc regressions revealed negative associations between $\Delta_{(post-pre)/pre} myoI/tCr$ in the ACC and head impacts with mean *g*-force thresholds of >110 and >120 *g* (**Appendix Table B.8**). Concussion diagnosis or collar did not significantly alter the relationship between either $\Delta_{(post-pre)/pre} tNAA/tCr$ (**Appendix Table B.9**) or $\Delta_{(post-pre)/pre} Glx/tCr$ (**Appendix Table B.10**) and head impacts for any mean *g*-force thresholds.

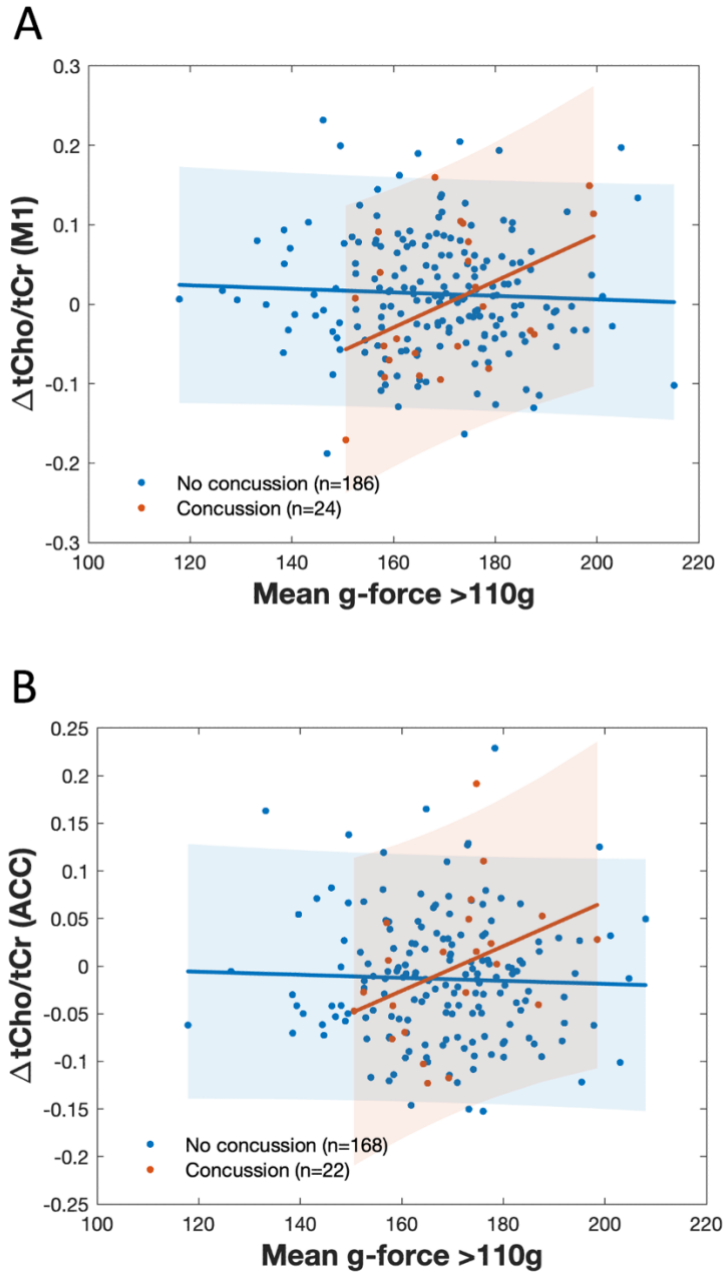


Figure 3.7. Univariate linear regressions between changes in tCho/tCr and mean g-force for threshold >110 g. The relationship between $\Delta_{(post-pre)/pre} tCho/tCr$ and head impacts varied significantly in M1 (A) at a mean g-force threshold of >110 g ($t=2.68, p=0.0080$) as well as for all thresholds between >80 g and >150 g (Appendix Table B.1), and in the ACC (B) at a threshold of >110 g ($t=2.02, p=0.045$) and at thresholds of >80, >100, >120, >130 and >140 g (Appendix Table B.6).

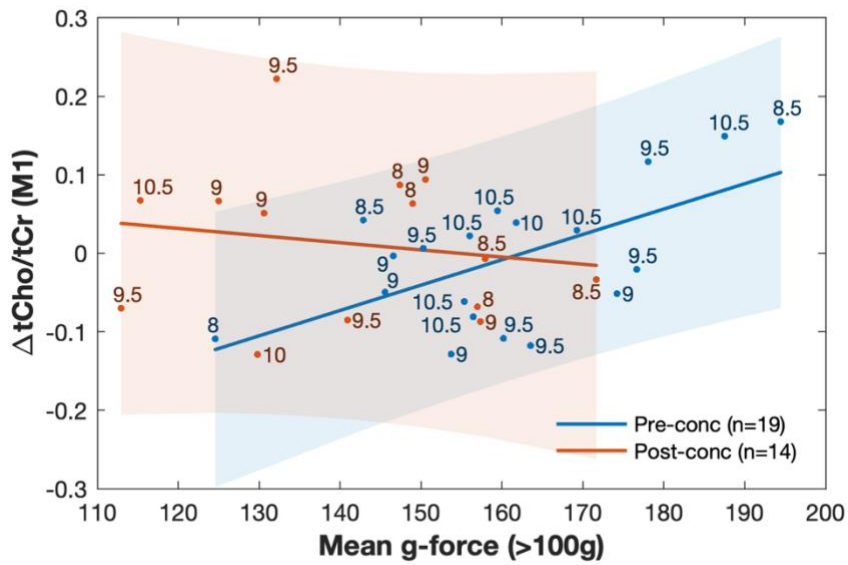


Figure 3.8. Relationships between changes in tCho/tCr in M1 and mean g-force of head impacts >100 g, between pre-season and post-concussion ('pre-conc', blue) and between post-concussion and post-season ('post-conc', orange). Each data point is labeled with time of concussion in half month increments (i.e., 8 = first half of August, 8.5 = second half of August, etc.).

CHAPTER 4

DISCUSSION

To our knowledge, this is the largest longitudinal MRS study of American high school football athletes to date. Across a single season of practice and games, significant differences were observed between pre-season and post-season timepoints in tCho/tCr, Glx/tCr and myoI/tCr for participants without a diagnosed concussion. The relationships between $\Delta_{(post-pre)/pre} tCho/tCr$ in both M1 and the ACC and head impacts varied significantly between participants with and without a diagnosed concussion at higher mean *g*-force thresholds. Post-hoc regressions revealed positive correlations between $\Delta_{(post-pre)/pre} tCho/tCr$ in M1 and head impacts at mean *g*-force thresholds of >100 *g* and >110 *g* in participants with a diagnosed concussion.

4.1 Associations Between Changes in tCho/tCr and Mean *g*-force Vary as a Function of Concussion Diagnosis

Increases in tCho/tCr may be associated with higher cell membrane turnover and may be regarded as an inflammatory response.²⁸ Significant associations between tCho/tCr and head impacts in the present study suggest tCho may be a key outcome metric for concussion in participants with impacts above a *g*-force threshold (e.g., 80 *g*). Prior studies have observed elevated Cho levels in subjects after a concussion compared to healthy controls at both the subacute (2 weeks - 3 months) and chronic (> 3 months) stages of injury, whereas no difference was observed between subjects with sub-concussive hits without a concussion or controls.¹⁴ In a cohort of 24 high school athletes,

tCho/tCr was also positively associated with head impacts at mean *g*-force threshold of >50 *g*, although a single time point measurement (mid-season) of tCho/tCr was used for the analysis.¹⁹

In participants with diagnosed concussion only, head impacts with mean *g*-force thresholds >100 and >110 *g* were significantly associated with increases in tCho/tCr in both M1 and the ACC, suggesting impacts with higher mean *g*-force may be associated with neurochemical changes over a period of a sports season in participants with a diagnosed concussion. Interestingly, in the post-hoc analysis, the relationship between changes in tCho/tCr in M1 and head impacts measured after concussion showed a different trend compared to the relationship measured before concussion at a mean *g*-force threshold of >100 *g*, suggesting the effect of concussion diagnosis on neurochemical alterations may also be observed on a subacute timeframe from weeks to months. Together, these results suggest a diagnosed concussion after repeated impacts may produce a distinct neurochemical response compared to repeated impacts in individuals without a concussion during a single sports season. Further investigation of brain metabolite changes across various times since injury is warranted.

4.2 tNAA/tCr Did Not Vary as a Function of Time, Concussion Diagnosis, Impacts, or Collar

Most prior studies of neurochemical changes in response to head impacts or concussion diagnosis have focused on changes in NAA as a metric for neuronal and axonal health²⁹; however, we did not observe differences in tNAA/tCr as a function of time, concussion diagnosis, collar. Decreases in tNAA in acute and chronic phase post-injury have been

consistently observed in collegiate and professional football athletes, suggesting metabolite markers of injury may be age dependent.^{13,30} Prior studies suggest continuous maturation of white matter throughout adolescence into adulthood,^{31,32} and the concentration of tNAA in white matter increases across the course of adolescence.³³ It is possible the changes in tNAA in adolescents are too small to detect with MRS due to lower tNAA concentrations compared to adults, or tNAA in the adolescent brain may be less sensitive to injury. We also did not observe a correlation between $\Delta_{(post-pre)/pre} tNAA/tCr$ and head impacts at any *g*-force threshold. This is consistent with prior work exploring sub-concussive head impacts in high school football athletes, where tNAA did not vary across the season and no correlations were observed between tNAA and head impacts.¹⁹ Further research into the effects of age and development on brain changes after injury is warranted.

4.3 Changes in myoI/tCr and Glx/tCr Vary as a Function of Concussion

Diagnosis and Collar

In M1, a decrease in myoI/tCr post-season compared to pre-season in participants without a diagnosed concussion was observed. This is consistent with observations in another cohort of high school American football athletes showing myoI concentrations were lower during mid- and post-season in the dorsolateral prefrontal cortex compared to baseline.¹⁸ Our previous work in a cohort of collegiate basketball players without a diagnosed concussion also reported a decrease in myoI/tCr between pre-season and mid-season¹⁷, suggesting myoI may be a marker of sub-concussive injury or other play-related factors.¹⁸

A significant increase in Glx/tCr in the ACC post-season compared to pre-season was observed in participants without a diagnosed concussion. No significant trends were observed between $\Delta_{(post-pre)/pre} Glx/tCr$ and head impacts. Reported changes in Glx after TBI are inconsistent as some studies report decreased Glx in M1 in high school football athletes^{14,18}, and we did not see changes in Glx in M1 as a function of time, concussion diagnosis, collar. A previous study using a cohort of mTBI patients with a range of injury types (e.g., fall, motor vehicle accident, sports-related injury, etc.) observed lower Glx concentrations in white matter and higher Glx concentrations in grey matter in mTBI patients approximately 4 months post-injury compared to 13 days post-injury.³⁴ Our MRS acquisition was within one week following diagnosed concussion during the hyperacute stage of injury,¹⁴ and may indicate transient effects on neurochemistry. It is possible some differences between the present study and past work are due to differences in time point of MRS acquisition.

Prior findings in this clinical trial suggested wearing a JVC collar may provide protection against alterations in white matter in high school athletes.²³ In this study, changes in myoI/tCr in the ACC were significantly and negatively associated with head impacts with mean *g*-force thresholds of >110 and >120 *g* in post-hoc analysis for the collar group only.

4.4 Limitations and Future Research

Limitations in this study include differences in practice regime across schools or teams which may have confounded the impact data. The effect of age was not considered but all athletes were adolescents. Variation due to differences in biological sex was not evaluated

as only male players were included in this study of football players. Differences across the three MR scanners may have introduced some variability; however, all participants were scanned on the same scanner for all repeated measurements. While mean *g*-force is harder to interpret than number of impacts, mean *g*-force accounts for both magnitude and number of head impacts. There was also no clear trend in the median number of hits across all mean *g*-force threshold values, suggesting head impacts with higher mean *g*-force values were not driven by isolated incidents or a few high impact hits. Importantly, no relationships were observed for impacts with mean *g*-force thresholds of less than 80 *g* for any metabolites, as lower thresholds included impacts encompassing a wider range of magnitudes, as well as reduced sensitivity of the accelerometer to lower forces. Lastly, MRS data were acquired largely in cortical regions selected due to the mechanism of action of the JVC collar to impact cerebral blood flow and time available within the MR exam. Consideration of metabolite changes in predominantly white matter regions is an important area of future investigation.

4.5 Conclusion

In conclusion, we observed the relationships between $\Delta_{(post-pre)/pre} tCho/tCr$ and head impacts at higher mean *g*-force thresholds varied significantly between participants with and without a diagnosed concussion. A significant and positive correlation was observed between $\Delta_{(post-pre)/pre} tCho/tCr$ and head impacts at mean *g*-force thresholds of >100 *g* and >110 *g*, suggesting *tCho/tCr* may be a key outcome metric for concussion as well as head impacts. The relationship between $\Delta_{(post-pre)/pre} myoI/tCr$ and head impacts varied between collar and non-collar groups, and *myoI/tCr* was significantly and

negatively correlated with impacts with mean *g*-force thresholds of >100, >110 and >120 *g*. Future work will consider the effect of age and biological sex on neurochemical changes in response to concussion, and other neurological outcomes, such as behavioral and cognitive performance, in relation to changes in brain metabolites.

CHAPTER 5

OTHER RESEARCH WORKS

To gain a holistic understanding of MRI research in brain injury, I have participated in two additional research projects during my master's degree. The first project was a systematic review in which I contributed to data collection and manuscript preparation. The goal of this review was to investigate demographic reporting in human brain MR research from 2010-2020. For the second research project, I am collecting data to facilitate MR-based brain thermometry measurements in patients after out of hospital cardiac arrest who are undergoing therapeutic hypothermia. In this chapter, an overview as well as a progress report for each project is provided.

5.1 Demographic Reporting of Human Neuroimaging Research

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Sterling E, Pearl H, Liu Z, Allen JW, Fleischer CC. Demographic reporting across a decade of neuroimaging: a systematic review. *Brain Imaging and Behavior*. 2022;16(6):2785-2796.

The rapid development of translational MRI technology and advancement requires an increasing number of neuro studies involving human subjects.³⁵ Although physiological differences in brain anatomy and morphology have been observed across sex, race and ethnicity, a lack of reporting of these demographic data are still observed.³⁵ Additionally, exclusion of women and minorities in clinical research continued even after the implementation of the NIH Revitalization Act of 1993, which provides guidelines for

demographic inclusions in NIH-funded research.³⁵ In order to understand current reporting of demographic diversity in neuroimaging research, we conducted a systematic review of brain MR studies from 2010 to 2020 conducted in the United States to investigate the demographic reporting and analyze the reported diversity in these research.³⁵ Key results indicate reported race and ethnicity were considerably underreported compared to reported sex, as shown in **Figure 5.1**, and the number of subjects identified as White exceeded more than 50% of all subjects in articles reporting race.³⁵ Challenges in reporting race and ethnicity of study subjects arise from time and resource constraints, recruitment methods including geographical bias and financial difficulties, among others.³⁵ Additionally, since subjects may identify with multiple races or ethnicities, it is challenging in clinical studies to delineate differences across race and ethnicity with clear classification and definition. In conclusion, although challenges in reporting demographics exist, efforts should be made for including more explicit demographic descriptors, considering variations due to sex, race and ethnicity, and pushing for more open-access demographic data.³⁵

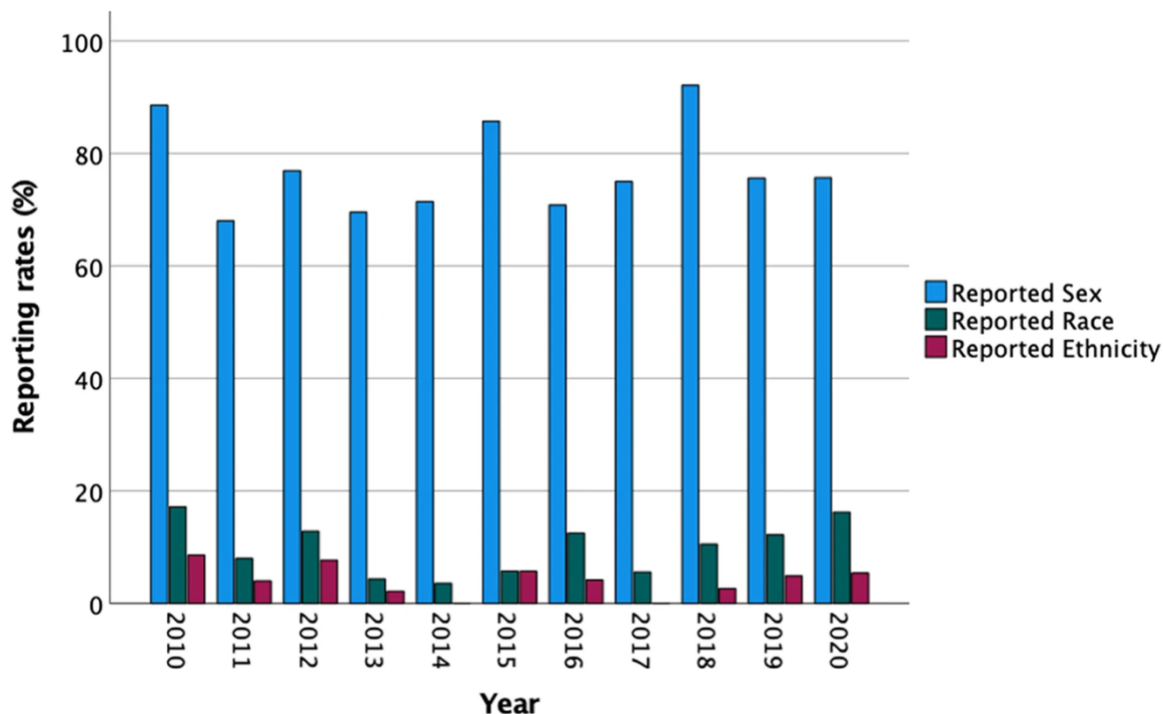


Figure 5.1. Demographic reporting rates in neuroimaging studies over time. Reporting rates, calculated as the number of articles with reported demographics out of the total number of included articles per year, are shown for sex, race, and ethnicity. No apparent trends over time were observed. The figure and figure caption were reproduced from Sterling E. et al in “Demographic reporting across a decade of neuroimaging: a systematic review” and used with permission under the CC-BY-4.0 license.

5.2 Brain Thermometry during Therapeutic Hypothermia

Thermal regulation is essential to brain health in human.³⁶ After ischemic brain injury, brain temperature is dysregulated and exceeds core body temperature.^{37,38} To avoid irreversible brain damage, a treatment option with the goal of lowering temperature in body circulation to provide neuroprotection and prevent further brain damage is therapeutic hypothermia.^{39,40} However, current clinical measurements of brain temperature rely largely on invasive surgical probing methods or MR proton shift

frequency phase mapping that calculates temperature change based on phase change.⁴¹ In this second ongoing project, I am implementing MR chemical shift thermometry (CST) in patients with out of hospital cardiac arrest or spinal cord injury who are prescribed therapeutic hypothermia to quantify brain temperature non-invasively. MR CST takes advantage of chemical shift properties of compounds in the brain (i.e., temperature-sensitive water peak and temperature-insensitive NAA peak) to calculate and map *in vivo* absolute brain temperature non-invasively in animals and human.^{42,43} Currently, cardiac arrest and spinal cord injury patients are recruited for single voxel spectroscopy and chemical shift imaging, and brain temperature will be calculated for each subject.

Appendix A

Appendix A

Group-wise Comparison Results

Table A.1. Changes in metabolites relative to tCr in M1 and in the ACC measured at pre-season and post-season in participants without a diagnosed concussion.

M1 metabolites					
	Median \pm SE (pre-season)	Median \pm SE (post-season)	W ^a	p	p _{FDR} ^b
tNAA/tCr	1.50 \pm 7.50 $\times 10^{-3}$	1.50 \pm 7.45 $\times 10^{-3}$	7871	0.26	0.26
tCho/tCr	1.88 $\times 10^{-1}$ \pm 1.33 $\times 10^{-3}$	1.88 $\times 10^{-1}$ \pm 1.32 $\times 10^{-3}$	7307	0.059	0.12
myoI/tCr	6.66 $\times 10^{-1}$ \pm 3.59 $\times 10^{-3}$	6.57 $\times 10^{-1}$ \pm 3.87 $\times 10^{-3}$	6892	0.014	0.057
Glx/tCr	1.08 \pm 7.45 $\times 10^{-3}$	1.07 \pm 7.83 $\times 10^{-3}$	7535	0.11	0.15
ACC metabolites					
tNAA/tCr	1.11 \pm 8.17 $\times 10^{-3}$	1.12 \pm 7.85 $\times 10^{-3}$	6415	0.28	0.28
tCho/tCr	2.33 $\times 10^{-1}$ \pm 1.40 $\times 10^{-3}$	2.27 $\times 10^{-1}$ \pm 1.47 $\times 10^{-3}$	4978	7.9$\times 10^{-4}$	3.1$\times 10^{-3}$
myoI/tCr	7.38 $\times 10^{-1}$ \pm 4.76 $\times 10^{-3}$	7.37 $\times 10^{-1}$ \pm 4.34 $\times 10^{-3}$	5889	0.056	0.074
Glx/tCr	1.60 \pm 8.75 $\times 10^{-3}$	1.63 \pm 1.08 $\times 10^{-2}$	5221	3.0$\times 10^{-3}$	5.9$\times 10^{-3}$

^aMetabolite differences between pre-season and post-season were calculated using Wilcoxon signed rank test

^bThe Benjamini-Hochberg method was used for false discovery rate (FDR) correction

Significant p-values determined by $p \leq 0.05$ are bolded

Sample size in M1 and in the ACC is n=186 and n=168, respectively

M1=primary motor cortex, ACC=anterior cingulate cortex, SE=standard error, tNAA=total *N*-acetylaspartate + *N*-acetylaspartyl glutamate, tCr=total creatine + phosphocreatine creatine, tCho=total glycerophosphocholine + phosphocholine, myoI=myo-inositol, Glx=glutamine + glutamate

Table A.2. Changes in metabolites relative to tCr in M1 and in the ACC measured at pre-season, post-concussion, and post-season in participants with a diagnosed concussion.

M1 metabolites						
	Median ± SE (pre-season)	Median ± SE (post-concussion)	Median ± SE (post-season)	c ^{2a}	p	p _{FDR} ^b
tNAA/tCr	1.52 ± 1.55×10⁻²	1.53 ± 1.64×10⁻²	1.52 ± 1.08×10⁻²	2.5	0.29	0.57
tCho/tCr	1.87×10⁻¹ ± 3.34×10⁻³	1.81×10⁻¹ ± 3.24×10⁻³	1.83×10⁻¹ ± 4.04×10⁻³	0.4	0.82	0.82
myoI/tCr	6.57×10⁻¹ ± 1.08×10⁻²	6.63×10⁻¹ ± 1.24×10⁻²	6.51×10⁻¹ ± 1.51×10⁻²	0.7	0.70	0.82
Glx/tCr	1.05 ± 2.67×10⁻²	1.11 ± 1.63×10⁻²	1.10 ± 1.60×10⁻²	3.6	0.17	0.57
ACC metabolites						
	Median ± SE (pre-season)	Median ± SE (post-concussion)	Median ± SE (post-season)	c ²	p	p _{FDR}
tNAA/tCr	1.12 ± 2.08×10⁻²	1.12 ± 2.23×10⁻²	1.10 ± 1.99×10⁻²	4.8	0.091	0.36
tCho/tCr	2.25×10⁻¹ ± 4.45×10⁻³	2.30×10⁻¹ ± 3.73×10⁻³	2.24×10⁻¹ ± 3.90×10⁻³	0	>0.99	>0.99
myoI/tCr	7.41×10⁻¹ ± 1.13×10⁻²	7.55×10⁻¹ ± 1.49×10⁻²	7.15×10⁻¹ ± 1.49×10⁻²	2.1	0.35	0.70
Glx/tCr	1.64 ± 2.73×10⁻²	1.65 ± 2.50×10⁻²	1.63 ± 3.10×10⁻²	1.3	0.52	0.70

^aMetabolite differences between pre-season, post-concussion and post-season were analyzed using Friedman's test

^bThe Benjamini-Hochberg method was used for false discovery rate (FDR) correction

Significant p-values determined by p ≤ 0.05 are bolded

Sample size in M1 and in the ACC is n=21 for both

M1=primary motor cortex, ACC=anterior cingulate cortex, SE=standard error, tNAA=total N-acetylaspartate + N-acetylaspartyl glutamate, tCr=total creatine + phosphocreatine creatine, tCho=total glycerophosphocholine + phosphocholine, myoI=myo-inositol, Glx=glutamine + glutamate

Table A.3. Differences in changes in metabolites/tCr in M1 and in the ACC between participants with and without a diagnosed concussion.

M1 metabolites^a					
	Median ± SE (no concussion)	Median ± SE (concussion)	U ^b	p	p _{FDR} ^c
tNAA/tCr	8.80×10 ⁻³ ± 4.11×10 ⁻³	8.41×10 ⁻³ ± 8.12×10 ⁻³	2224	0.98	0.98
tCho/tCr	8.06×10 ⁻³ ± 5.36×10 ⁻³	-1.81×10 ⁻² ± 1.82×10 ⁻²	2009	0.43	0.78
myoI/tCr	-6.85×10 ⁻³ ± 4.48×10 ⁻³	-1.87×10 ⁻² ± 1.57×10 ⁻²	2078	0.58	0.78
Glx/tCr	-5.56×10 ⁻³ ± 6.29×10 ⁻³	2.05×10 ⁻² ± 2.32×10 ⁻²	1970	0.35	0.78
ACC metabolites					
tNAA/tCr	3.25×10 ⁻³ ± 6.53×10 ⁻³	-3.39×10 ⁻² ± 1.96×10 ⁻²	1406	0.069	0.27
tCho/tCr	-1.39×10 ⁻² ± 5.02×10 ⁻³	4.01×10 ⁻³ ± 1.58×10 ⁻²	1677	0.48	0.48
myoI/tCr	-5.01×10 ⁻³ ± 6.06×10 ⁻³	-3.02×10 ⁻² ± 1.48×10 ⁻²	1602	0.31	0.42
Glx/tCr	1.64×10 ⁻² ± 6.43×10 ⁻³	-9.77×10 ⁻³ ± 1.76×10 ⁻²	1538	0.20	0.40

^aMetabolites/tCr were normalized to pre-season baseline, calculated as (post-season – pre-season)/pre-season

^bGroup-wise comparisons are calculated with Mann Whitney *U* test

^cThe Benjamini-Hochberg method was used for false discovery rate (FDR) correction

Significant p-values determined by p ≤ 0.05 are bolded

Sample size in M1 is n=24 (concussion) and n=186 (no concussion), and in the ACC is n=22 (concussion) and n=168 (no concussion)

M1=primary motor cortex, ACC=anterior cingulate cortex, SE=standard error, tNAA=total *N*-acetylaspartate + *N*-acetylaspartyl glutamate, tCr=total creatine + phosphocreatine creatine, tCho=total glycerophosphocholine + phosphocholine, myoI=myo-inositol, Glx=glutamine + glutamate

Table A.4. Differences in changes in metabolites/tCr in M1 and in the ACC between collar and non-collar groups.

M1 metabolites^a					
	Median ± SE (collar)	Median ± SE (non-collar)	U ^b	p	p _{FDR} ^c
tNAA/tCr	9.88×10 ⁻³ ± 4.74×10 ⁻³	8.80×10 ⁻³ ± 5.92×10 ⁻³	5053	0.31	0.62
tCho/tCr	1.06×10 ⁻² ± 7.23×10 ⁻³	1.92×10 ⁻³ ± 7.35×10 ⁻³	5029	0.28	0.62
myoI/tCr	-5.72×10 ⁻³ ± 6.02×10 ⁻³	-1.30×10 ⁻² ± 6.29×10 ⁻³	5398	0.82	0.82
Glx/tCr	-8.10×10 ⁻³ ± 8.74×10 ⁻³	-2.47×10 ⁻³ ± 8.69×10 ⁻³	5228	0.54	0.72
ACC metabolites					
tNAA/tCr	1.31×10 ⁻² ± 8.64×10 ⁻³	-1.14×10 ⁻² ± 8.95×10 ⁻³	3882	0.10	0.40
tCho/tCr	-1.29×10 ⁻² ± 6.54×10 ⁻³	-1.52×10 ⁻² ± 7.10×10 ⁻³	4455	0.90	0.93
myoI/tCr	-1.26×10 ⁻² ± 8.14×10 ⁻³	-5.06×10 ⁻³ ± 7.85×10 ⁻³	4472	0.93	0.93
Glx/tCr	8.51×10 ⁻³ ± 8.77×10 ⁻³	1.04×10 ⁻² ± 8.44×10 ⁻³	4384	0.75	0.93

^aMetabolites/tCr were normalized to pre-season baseline, calculated as (post-season – pre-season)/pre-season

^bGroup-wise comparisons are calculated with Mann Whitney *U* test

^cThe Benjamini-Hochberg method was used for false discovery rate (FDR) correction

Significant p-values determined by p ≤ 0.05 are bolded

Sample size in M1 is n=110 (collar) and n=100 (non-collar), and in the ACC is n=99 (collar) and n=91 (non-collar)

M1=primary motor cortex, ACC=anterior cingulate cortex, SE=standard error, tNAA=total *N*-acetylaspartate + *N*-acetylaspartyl glutamate, tCr=total creatine + phosphocreatine creatine, tCho=total glycerophosphocholine + phosphocholine, myoI=myo-inositol, Glx=glutamine + glutamate

Appendix B

Appendix B

Linear Regression Analysis Results

Table B.1. Linear regression analysis of $\Delta_{(postseason-preseason)}/preseason$ *tCho/tCr* in M1 and head impacts, concussion, and collar across all mean *g*-force thresholds.

<i>g</i> -force thresholds	Parameters	β^a	t	p
>20 <i>g</i>	<i>g</i> -force	1.0×10^{-4}	6.7×10^{-2}	0.95
	<i>g</i> -force \times concussion	-9.0×10^{-4}	-0.28	0.78
	<i>g</i> -force \times collar	-1.6×10^{-3}	-0.68	0.50
>30 <i>g</i>	<i>g</i> -force	-2.8×10^{-4}	-0.27	0.79
	<i>g</i> -force \times concussion	2.3×10^{-3}	1.11	0.27
	<i>g</i> -force \times collar	-7.4×10^{-4}	-0.49	0.62
>40 <i>g</i>	<i>g</i> -force	-6.2×10^{-4}	-0.73	0.47
	<i>g</i> -force \times concussion	1.3×10^{-3}	0.70	0.49
	<i>g</i> -force \times collar	5.3×10^{-4}	0.45	0.65
>50 <i>g</i>	<i>g</i> -force	-8.4×10^{-4}	-1.15	0.25
	<i>g</i> -force \times concussion	2.0×10^{-3}	1.31	0.19
	<i>g</i> -force \times collar	5.2×10^{-4}	0.53	0.60
>60 <i>g</i>	<i>g</i> -force	-2.9×10^{-4}	-0.46	0.65
	<i>g</i> -force \times concussion	2.2×10^{-3}	1.51	0.13
	<i>g</i> -force \times collar	-2.1×10^{-4}	-0.25	0.80
>70 <i>g</i>	<i>g</i> -force	-5.8×10^{-4}	-0.98	0.33
	<i>g</i> -force \times concussion	2.4×10^{-3}	1.75	8.2×10^{-2}
	<i>g</i> -force \times collar	-1.2×10^{-4}	-0.15	0.88
>80 <i>g</i>	<i>g</i> -force	-4.8×10^{-4}	-0.84	0.40
	<i>g</i> -force \times concussion	3.1×10^{-3}	2.40	1.7×10^{-2}
	<i>g</i> -force \times collar	-2.5×10^{-4}	-0.34	0.74
>90 <i>g</i>	<i>g</i> -force	-1.8×10^{-4}	-0.33	0.74
	<i>g</i> -force \times concussion	2.9×10^{-3}	2.23	2.7×10^{-2}
	<i>g</i> -force \times collar	2.4×10^{-6}	3.3×10^{-3}	1.00
>100 <i>g</i>	<i>g</i> -force	-2.5×10^{-4}	-0.45	0.65
	<i>g</i> -force \times concussion	3.9×10^{-3}	3.10	2.2×10^{-3}
	<i>g</i> -force \times collar	-1.7×10^{-5}	-2.3×10^{-2}	0.98
>110 <i>g</i>	<i>g</i> -force	-2.7×10^{-4}	-0.57	0.57
	<i>g</i> -force \times concussion	3.3×10^{-3}	2.68	8.0×10^{-3}
	<i>g</i> -force \times collar	-3.8×10^{-5}	-5.7×10^{-2}	0.95
>120 <i>g</i>	<i>g</i> -force	-2.7×10^{-4}	-0.65	0.52
	<i>g</i> -force \times concussion	2.8×10^{-3}	2.51	1.3×10^{-2}
	<i>g</i> -force \times collar	-3.0×10^{-5}	-5.2×10^{-2}	0.96
>130 <i>g</i>	<i>g</i> -force	-3.4×10^{-6}	-8.8×10^{-3}	0.99
	<i>g</i> -force \times concussion	2.3×10^{-3}	2.17	3.1×10^{-2}
	<i>g</i> -force \times collar	-5.4×10^{-4}	-0.92	0.36
>140 <i>g</i>	<i>g</i> -force	1.1×10^{-4}	0.28	0.78
	<i>g</i> -force \times concussion	2.1×10^{-3}	2.04	4.2×10^{-2}
	<i>g</i> -force \times collar	-9.3×10^{-4}	-1.64	0.10
>150 <i>g</i>	<i>g</i> -force	3.0×10^{-4}	0.80	0.43
	<i>g</i> -force \times concussion	6.2×10^{-4}	0.72	0.47
	<i>g</i> -force \times collar	-9.4×10^{-4}	-1.77	0.08

^aEstimated coefficients, t-statistics and p-values are calculated with univariate linear regression

M1=primary motor cortex, tCr=total creatine + phosphocreatine, tCho=total glycerophosphocholine + phosphocholine

Significant p-values determined by $p \leq 0.05$ are bolded

Table B.2. Post-hoc regressions of metabolites in M1 and mean g-force threshold of head impacts.

Metabolites	g-force thresholds	Groups	Coefficients ^a	t	p
tCho/tCr	>80 g	Concussion	2.3×10^{-3}	1.65	0.11
		No concussion	-4.9×10^{-4}	-1.33	0.19
	>90 g	Concussion	2.7×10^{-3}	1.91	6.9×10^{-2}
		No concussion	-9.6×10^{-5}	-0.27	0.79
	>100 g	Concussion	3.6×10^{-3}	2.85	9.3×10^{-3}
		No concussion	-1.6×10^{-4}	-0.43	0.67
	>110 g	Concussion	2.9×10^{-3}	2.28	3.3×10^{-2}
		No concussion	-2.2×10^{-4}	-0.66	0.51
	>120 g	Concussion	2.4×10^{-3}	2.00	5.8×10^{-2}
		No concussion	-2.5×10^{-4}	-0.83	0.41
	>130 g	Concussion	1.8×10^{-3}	1.64	0.12
		No concussion	-1.7×10^{-4}	-0.58	0.56
	>140 g	Concussion	1.5×10^{-3}	1.30	0.21
		No concussion	-2.9×10^{-4}	-1.01	0.31

^aEstimated coefficients, t-statistics and p-values are calculated with univariate linear regression

M1=primary motor cortex, tCr=total creatine + phosphocreatine, tCho=total glycerophosphocholine + phosphocholine

Significant p-values determined by $p \leq 0.05$ are bolded

Table B.3. Linear regression analysis of $\Delta_{(postseason-preseason)}/preseason$ $tNAA/tCr$ in M1 and head impacts, concussion, and collar across all mean g -force thresholds.

g -force thresholds	Parameters	β^a	t	p
>20 g	g -force	2.0×10^{-4}	0.18	0.86
	g -force \times concussion	1.4×10^{-3}	0.60	0.55
	g -force \times collar	-4.2×10^{-4}	-0.25	0.80
>30 g	g -force	-6.4×10^{-5}	-8.3×10^{-2}	0.93
	g -force \times concussion	1.9×10^{-3}	1.23	0.22
	g -force \times collar	-2.3×10^{-4}	-0.21	0.83
>40 g	g -force	-1.6×10^{-4}	-0.26	0.79
	g -force \times concussion	1.4×10^{-3}	1.09	0.28
	g -force \times collar	3.0×10^{-4}	0.35	0.73
>50 g	g -force	-2.5×10^{-4}	-0.47	0.64
	g -force \times concussion	1.1×10^{-3}	1.00	0.32
	g -force \times collar	4.8×10^{-4}	0.67	0.50
>60 g	g -force	-4.2×10^{-4}	-0.89	0.37
	g -force \times concussion	1.2×10^{-3}	1.11	0.27
	g -force \times collar	4.9×10^{-4}	0.80	0.43
>70 g	g -force	-3.8×10^{-4}	-0.87	0.39
	g -force \times concussion	1.1×10^{-3}	1.08	0.28
	g -force \times collar	6.1×10^{-4}	1.06	0.29
>80 g	g -force	-2.2×10^{-4}	-0.52	0.60
	g -force \times concussion	1.1×10^{-3}	1.13	0.26
	g -force \times collar	4.8×10^{-4}	0.87	0.39
>90 g	g -force	-6.3×10^{-4}	-1.56	0.12
	g -force \times concussion	7.9×10^{-4}	0.83	0.41
	g -force \times collar	1.0×10^{-3}	1.95	5.2×10^{-2}
>100 g	g -force	-4.8×10^{-4}	-1.18	0.24
	g -force \times concussion	7.0×10^{-4}	0.75	0.46
	g -force \times collar	7.9×10^{-4}	1.46	0.15
>110 g	g -force	-2.5×10^{-4}	-0.70	0.49
	g -force \times concussion	6.2×10^{-4}	0.68	0.50
	g -force \times collar	6.0×10^{-4}	1.21	0.23
>120 g	g -force	-2.1×10^{-4}	-0.69	0.49
	g -force \times concussion	3.9×10^{-4}	0.47	0.64
	g -force \times collar	3.3×10^{-4}	0.75	0.45
>130 g	g -force	-9.0×10^{-5}	-0.32	0.75
	g -force \times concussion	2.1×10^{-4}	0.28	0.78
	g -force \times collar	3.2×10^{-5}	7.5×10^{-2}	0.94
>140 g	g -force	-1.7×10^{-4}	-0.58	0.56
	g -force \times concussion	5.2×10^{-4}	0.68	0.49
	g -force \times collar	-4.9×10^{-5}	-0.12	0.91
>150 g	g -force	4.6×10^{-5}	0.17	0.87
	g -force \times concussion	2.9×10^{-4}	0.45	0.65
	g -force \times collar	-2.2×10^{-4}	-0.57	0.57

^aEstimated coefficients, t-statistics and p-values are calculated with univariate linear regression
M1=primary motor cortex, tCr=total creatine + phosphocreatine, tNAA=total *N*-acetylaspartate + *N*-acetylaspartyl glutamate
Significant p-values determined by $p \leq 0.05$ are bolded

Table B.4. Linear regression analysis of $\Delta_{(postseason-preseason)}/preseason$ *myoI/tCr* in M1 and head impacts, concussion, and collar across all mean *g*-force thresholds.

<i>g</i> -force thresholds	Parameters	β^a	t	p
>20 <i>g</i>	<i>g</i> -force	-1.1×10 ⁻³	-0.80	0.42
	<i>g</i> -force × concussion	2.6×10 ⁻³	0.97	0.33
	<i>g</i> -force × collar	5.8×10 ⁻⁴	0.30	0.77
>30 <i>g</i>	<i>g</i> -force	-5.6×10 ⁻⁴	-0.62	0.54
	<i>g</i> -force × concussion	1.9×10 ⁻³	1.11	0.27
	<i>g</i> -force × collar	6.0×10 ⁻⁴	0.47	0.64
>40 <i>g</i>	<i>g</i> -force	-5.8×10 ⁻⁴	-0.79	0.43
	<i>g</i> -force × concussion	1.2×10 ⁻³	0.76	0.45
	<i>g</i> -force × collar	8.6×10 ⁻⁴	0.87	0.39
>50 <i>g</i>	<i>g</i> -force	-3.1×10 ⁻⁴	-0.50	0.61
	<i>g</i> -force × concussion	1.1×10 ⁻³	0.86	0.39
	<i>g</i> -force × collar	5.9×10 ⁻⁴	0.71	0.48
>60 <i>g</i>	<i>g</i> -force	-2.2×10 ⁻⁴	-0.40	0.69
	<i>g</i> -force × concussion	1.2×10 ⁻³	0.93	0.35
	<i>g</i> -force × collar	3.3×10 ⁻⁴	0.45	0.65
>70 <i>g</i>	<i>g</i> -force	-2.0×10 ⁻⁴	-0.40	0.69
	<i>g</i> -force × concussion	1.2×10 ⁻³	0.98	0.33
	<i>g</i> -force × collar	2.8×10 ⁻⁵	0.04	0.97
>80 <i>g</i>	<i>g</i> -force	-3.5×10 ⁻⁴	-0.73	0.47
	<i>g</i> -force × concussion	1.4×10 ⁻³	1.24	0.22
	<i>g</i> -force × collar	2.0×10 ⁻⁴	0.32	0.75
>90 <i>g</i>	<i>g</i> -force	2.7×10 ⁻⁴	0.57	0.57
	<i>g</i> -force × concussion	4.3×10 ⁻⁴	0.38	0.70
	<i>g</i> -force × collar	-2.8×10 ⁻⁴	-0.46	0.65
>100 <i>g</i>	<i>g</i> -force	1.2×10 ⁻⁴	0.26	0.80
	<i>g</i> -force × concussion	1.3×10 ⁻³	1.17	0.24
	<i>g</i> -force × collar	-2.7×10 ⁻⁴	-0.43	0.67
>110 <i>g</i>	<i>g</i> -force	2.5×10 ⁻⁴	0.60	0.55
	<i>g</i> -force × concussion	7.5×10 ⁻⁴	0.71	0.48
	<i>g</i> -force × collar	-4.0×10 ⁻⁴	-0.69	0.49
>120 <i>g</i>	<i>g</i> -force	-1.2×10 ⁻⁴	-0.34	0.74
	<i>g</i> -force × concussion	1.1×10 ⁻³	1.18	0.24
	<i>g</i> -force × collar	2.8×10 ⁻⁴	0.56	0.58
>130 <i>g</i>	<i>g</i> -force	-1.6×10 ⁻⁴	-0.50	0.62
	<i>g</i> -force × concussion	1.2×10 ⁻³	1.33	0.19
	<i>g</i> -force × collar	4.3×10 ⁻⁴	0.88	0.38
>140 <i>g</i>	<i>g</i> -force	-3.8×10 ⁻⁴	-1.08	0.28
	<i>g</i> -force × concussion	1.0×10 ⁻³	1.18	0.24
	<i>g</i> -force × collar	6.2×10 ⁻⁴	1.28	0.20
>150 <i>g</i>	<i>g</i> -force	-2.7×10 ⁻⁴	-0.85	0.40
	<i>g</i> -force × concussion	7.7×10 ⁻⁴	1.05	0.30
	<i>g</i> -force × collar	2.0×10 ⁻⁴	0.44	0.66

^aEstimated coefficients, t-statistics and p-values are calculated with univariate linear regression
M1=primary motor cortex, tCr=total creatine + phosphocreatine creatine, myoI=myo-inositol
Significant p-values determined by $p \leq 0.05$ are bolded

Table B.5. Linear regression analysis of $\Delta_{(postseason-preseason)}/preseason$ Glx/tCr in M1 and head impacts, concussion, and collar across all mean g-force thresholds.

g-force thresholds	Parameters	β^a	t	p
>20 g	g-force	2.0×10^{-3}	1.08	0.28
	g-force \times concussion	-4.6×10^{-3}	-1.23	0.22
	g-force \times collar	-4.2×10^{-3}	-1.54	0.13
>30 g	g-force	8.7×10^{-4}	0.68	0.50
	g-force \times concussion	-2.7×10^{-3}	-1.09	0.28
	g-force \times collar	-2.4×10^{-3}	-1.33	0.19
>40 g	g-force	6.4×10^{-4}	0.62	0.53
	g-force \times concussion	-2.2×10^{-3}	-1.03	0.31
	g-force \times collar	-1.4×10^{-3}	-1.03	0.31
>50 g	g-force	2.1×10^{-4}	0.24	0.81
	g-force \times concussion	-1.9×10^{-3}	-1.03	0.30
	g-force \times collar	-3.8×10^{-4}	-0.33	0.74
>60 g	g-force	-3.8×10^{-4}	-0.49	0.63
	g-force \times concussion	-1.2×10^{-3}	-0.67	0.50
	g-force \times collar	6.9×10^{-4}	0.67	0.50
>70 g	g-force	-2.0×10^{-4}	-0.28	0.78
	g-force \times concussion	-9.2×10^{-4}	-0.55	0.58
	g-force \times collar	3.1×10^{-4}	0.33	0.74
>80 g	g-force	1.7×10^{-5}	2.5×10^{-2}	0.98
	g-force \times concussion	-4.5×10^{-4}	-0.29	0.77
	g-force \times collar	-9.6×10^{-6}	-1.1×10^{-2}	0.99
>90 g	g-force	-3.5×10^{-4}	-0.52	0.60
	g-force \times concussion	-7.3×10^{-4}	-0.46	0.65
	g-force \times collar	1.4×10^{-4}	0.16	0.88
>100 g	g-force	-3.5×10^{-4}	-0.52	0.60
	g-force \times concussion	-2.4×10^{-5}	-1.5×10^{-2}	0.99
	g-force \times collar	1.1×10^{-4}	0.12	0.90
>110 g	g-force	-3.3×10^{-4}	-0.56	0.58
	g-force \times concussion	5.8×10^{-4}	0.39	0.70
	g-force \times collar	-4.1×10^{-4}	-0.50	0.62
>120 g	g-force	-2.4×10^{-4}	-0.47	0.64
	g-force \times concussion	1.3×10^{-3}	0.93	0.35
	g-force \times collar	-4.6×10^{-4}	-0.64	0.52
>130 g	g-force	-3.7×10^{-5}	-8.1×10^{-2}	0.94
	g-force \times concussion	8.5×10^{-4}	0.68	0.50
	g-force \times collar	-1.0×10^{-3}	-1.46	0.15
>140 g	g-force	-1.4×10^{-4}	-0.28	0.78
	g-force \times concussion	5.6×10^{-4}	0.46	0.65
	g-force \times collar	-6.5×10^{-4}	-0.95	0.34
>150 g	g-force	-2.3×10^{-4}	-0.52	0.61
	g-force \times concussion	9.0×10^{-4}	0.87	0.39
	g-force \times collar	5.4×10^{-5}	8.5×10^{-2}	0.93

^aEstimated coefficients, t-statistics and p-values are calculated with univariate linear regression
M1=primary motor cortex, tCr=total creatine + phosphocreatine creatine, Glx=glutamine + glutamate
Significant p-values determined by $p \leq 0.05$ are bolded

Table B.6. Linear regression analysis of $\Delta_{(postseason-preseason)}/preseason$ tCho/tCr in the ACC and head impacts, concussion, and collar across all mean g-force thresholds.

g-force thresholds	Parameters	β^a	t	p
>20 g	g-force	-1.4×10^{-3}	-0.96	0.34
	g-force \times concussion	1.9×10^{-3}	0.64	0.52
	g-force \times collar	8.2×10^{-4}	0.38	0.70
>30 g	g-force	-7.6×10^{-4}	-0.75	0.45
	g-force \times concussion	2.8×10^{-3}	1.32	0.19
	g-force \times collar	1.9×10^{-4}	0.13	0.89
>40 g	g-force	-7.1×10^{-4}	-0.88	0.38
	g-force \times concussion	2.1×10^{-3}	1.09	0.28
	g-force \times collar	1.4×10^{-4}	0.12	0.90
>50 g	g-force	-7.0×10^{-4}	-1.01	0.31
	g-force \times concussion	1.7×10^{-3}	1.03	0.30
	g-force \times collar	1.1×10^{-4}	0.12	0.91
>60 g	g-force	-1.6×10^{-4}	-0.26	0.79
	g-force \times concussion	1.6×10^{-3}	1.04	0.30
	g-force \times collar	-4.7×10^{-4}	-0.60	0.55
>70 g	g-force	-1.6×10^{-4}	-0.30	0.77
	g-force \times concussion	2.1×10^{-3}	1.52	0.13
	g-force \times collar	-7.3×10^{-4}	-1.01	0.31
>80 g	g-force	4.8×10^{-5}	8.9×10^{-2}	0.93
	g-force \times concussion	2.7×10^{-3}	2.12	3.5×10^{-2}
	g-force \times collar	-7.4×10^{-4}	-1.06	0.29
>90 g	g-force	1.3×10^{-4}	0.24	0.81
	g-force \times concussion	1.4×10^{-3}	1.05	0.29
	g-force \times collar	-5.7×10^{-4}	-0.82	0.41
>100 g	g-force	1.6×10^{-4}	0.28	0.78
	g-force \times concussion	2.6×10^{-3}	2.00	4.8×10^{-2}
	g-force \times collar	-6.5×10^{-4}	-0.90	0.37
>110 g	g-force	1.2×10^{-4}	0.23	0.82
	g-force \times concussion	2.5×10^{-3}	2.02	4.5×10^{-2}
	g-force \times collar	-4.6×10^{-4}	-0.68	0.49
>120 g	g-force	-5.3×10^{-5}	-0.11	0.91
	g-force \times concussion	2.3×10^{-3}	2.07	4.0×10^{-2}
	g-force \times collar	-2.2×10^{-4}	-0.36	0.72
>130 g	g-force	-1.1×10^{-4}	-0.25	0.80
	g-force \times concussion	2.1×10^{-3}	2.17	3.1×10^{-2}
	g-force \times collar	-6.2×10^{-4}	-1.08	0.28
>140 g	g-force	-3.4×10^{-5}	-0.08	0.93
	g-force \times concussion	2.2×10^{-3}	2.39	1.8×10^{-2}
	g-force \times collar	-5.7×10^{-4}	-1.05	0.30
>150 g	g-force	-1.2×10^{-4}	-0.34	0.73
	g-force \times concussion	8.2×10^{-4}	1.07	0.29
	g-force \times collar	-2.4×10^{-4}	-0.49	0.62

^aEstimated coefficients, t-statistics and p-values are calculated with univariate linear regression
ACC=anterior cingulate cortex, tCr=total creatine + phosphocreatine creatine, tCho=total glycerophosphocholine + phosphocholine
Significant p-values determined by $p \leq 0.05$ are bolded

Table B.7. Linear regression analysis of $\Delta_{(postseason-preseason)}/preseason$ *myoI/tCr* in the ACC and head impacts, concussion, and collar across all mean *g*-force thresholds.

<i>g</i> -force thresholds	Parameters	β^a	t	p
>20 <i>g</i>	<i>g</i> -force	-1.3×10^{-3}	-0.79	0.43
	<i>g</i> -force \times concussion	-4.3×10^{-4}	-0.12	0.90
	<i>g</i> -force \times collar	-2.2×10^{-3}	-0.88	0.38
>30 <i>g</i>	<i>g</i> -force	-3.5×10^{-4}	-0.30	0.76
	<i>g</i> -force \times concussion	1.1×10^{-3}	0.43	0.67
	<i>g</i> -force \times collar	-2.5×10^{-3}	-1.49	0.14
>40 <i>g</i>	<i>g</i> -force	-1.2×10^{-4}	-0.13	0.89
	<i>g</i> -force \times concussion	1.8×10^{-3}	0.82	0.41
	<i>g</i> -force \times collar	-2.1×10^{-3}	-1.59	0.11
>50 <i>g</i>	<i>g</i> -force	1.5×10^{-4}	0.19	0.85
	<i>g</i> -force \times concussion	2.1×10^{-3}	1.12	0.27
	<i>g</i> -force \times collar	-2.0×10^{-3}	-1.90	5.9×10^{-2}
>60 <i>g</i>	<i>g</i> -force	1.1×10^{-4}	0.15	0.88
	<i>g</i> -force \times concussion	2.4×10^{-3}	1.37	0.17
	<i>g</i> -force \times collar	-1.5×10^{-3}	-1.69	9.2×10^{-2}
>70 <i>g</i>	<i>g</i> -force	-4.7×10^{-5}	-7.3×10^{-2}	0.94
	<i>g</i> -force \times concussion	1.5×10^{-3}	0.92	0.36
	<i>g</i> -force \times collar	-1.2×10^{-3}	-1.40	0.16
>80 <i>g</i>	<i>g</i> -force	3.4×10^{-4}	0.53	0.59
	<i>g</i> -force \times concussion	1.5×10^{-3}	0.99	0.33
	<i>g</i> -force \times collar	-1.5×10^{-3}	-1.84	6.7×10^{-2}
>90 <i>g</i>	<i>g</i> -force	2.2×10^{-4}	0.35	0.73
	<i>g</i> -force \times concussion	2.2×10^{-3}	1.45	0.15
	<i>g</i> -force \times collar	-1.2×10^{-3}	-1.45	0.15
>100 <i>g</i>	<i>g</i> -force	1.6×10^{-4}	0.25	0.80
	<i>g</i> -force \times concussion	2.6×10^{-3}	1.71	8.9×10^{-2}
	<i>g</i> -force \times collar	-1.6×10^{-3}	-1.90	5.9×10^{-2}
>110 <i>g</i>	<i>g</i> -force	4.1×10^{-4}	0.68	0.50
	<i>g</i> -force \times concussion	1.3×10^{-3}	0.91	0.36
	<i>g</i> -force \times collar	-1.6×10^{-3}	-2.09	3.8×10^{-2}
>120 <i>g</i>	<i>g</i> -force	5.2×10^{-4}	0.92	0.36
	<i>g</i> -force \times concussion	1.7×10^{-3}	1.34	0.18
	<i>g</i> -force \times collar	-1.8×10^{-3}	-2.47	1.4×10^{-2}
>130 <i>g</i>	<i>g</i> -force	3.5×10^{-4}	0.72	0.47
	<i>g</i> -force \times concussion	1.5×10^{-3}	1.29	0.20
	<i>g</i> -force \times collar	-1.3×10^{-3}	-2.00	4.7×10^{-2}
>140 <i>g</i>	<i>g</i> -force	2.9×10^{-6}	5.8×10^{-3}	1.00
	<i>g</i> -force \times concussion	2.1×10^{-3}	1.92	5.6×10^{-2}
	<i>g</i> -force \times collar	-9.9×10^{-4}	-1.52	0.13
>150 <i>g</i>	<i>g</i> -force	2.6×10^{-4}	0.60	0.55
	<i>g</i> -force \times concussion	1.2×10^{-3}	1.36	0.18
	<i>g</i> -force \times collar	-1.0×10^{-3}	-1.77	7.9×10^{-2}

^aEstimated coefficients, t-statistics and p-values are calculated with univariate linear regression
ACC=anterior cingulate cortex, tCr=total creatine + phosphocreatine creatine, myoI=myo-inositol
Significant p-values determined by $p \leq 0.05$ are bolded

Table B.8. Post-hoc regressions of metabolites in the ACC and mean g-force threshold of head impacts.

Metabolites	g-force thresholds	Groups	Coefficients ^a	t	p
tCho/tCr	>80 g	Concussion	2.3×10^{-3}	1.71	0.10
		No concussion	-3.9×10^{-4}	-1.13	0.26
	>100 g	Concussion	2.4×10^{-3}	1.74	0.10
		No concussion	-2.4×10^{-4}	-0.68	0.50
	>110 g	Concussion	2.3×10^{-3}	1.82	8.4×10^{-2}
		No concussion	-1.6×10^{-4}	-0.48	0.63
	>120 g	Concussion	2.1×10^{-3}	1.88	7.5×10^{-2}
		No concussion	-1.9×10^{-4}	-0.63	0.53
	>130 g	Concussion	1.6×10^{-3}	1.56	0.13
		No concussion	-4.2×10^{-4}	-1.44	0.15
	>140 g	Concussion	1.8×10^{-3}	1.82	8.4×10^{-2}
		No concussion	-3.5×10^{-4}	-1.30	0.20
myo-I/tCr	>110 g	Collar	-1.1×10^{-3}	-2.09	3.9×10^{-2}
		Non-collar	3.8×10^{-4}	0.65	0.51
	>120 g	Collar	-1.1×10^{-3}	-2.37	2.0×10^{-2}
		Non-collar	5.4×10^{-4}	1.02	0.31
	>130 g	Collar	-7.8×10^{-4}	-1.62	0.11
		Non-collar	3.9×10^{-4}	0.83	0.41

^aEstimated coefficients, t-statistics and p-values are calculated with univariate linear regression

ACC=anterior cingulate cortex, tCr=total creatine + phosphocreatine creatine, tCho=total glycerophosphocholine + phosphocholine, myoI=myo-inositol, Glx=glutamine + glutamate

Significant p-values determined by $p \leq 0.05$ are bolded

Table B.9. Linear regression analysis of $\Delta_{(postseason-preseason)}/preseason$ *tNAA/tCr* in the ACC and head impacts, concussion, and collar across all mean *g*-force thresholds.

<i>g</i> -force thresholds	Parameters	β^a	t	p
>20 <i>g</i>	<i>g</i> -force	2.2×10^{-3}	1.19	0.23
	<i>g</i> -force \times concussion	-5.9×10^{-3}	-1.54	0.12
	<i>g</i> -force \times collar	-3.3×10^{-3}	-1.20	0.23
>30 <i>g</i>	<i>g</i> -force	1.9×10^{-3}	1.50	0.14
	<i>g</i> -force \times concussion	-3.7×10^{-3}	-1.36	0.17
	<i>g</i> -force \times collar	-2.2×10^{-3}	-1.23	0.22
>40 <i>g</i>	<i>g</i> -force	1.5×10^{-3}	1.42	0.16
	<i>g</i> -force \times concussion	-2.9×10^{-3}	-1.19	0.23
	<i>g</i> -force \times collar	-1.2×10^{-3}	-0.85	0.40
>50 <i>g</i>	<i>g</i> -force	8.0×10^{-4}	0.90	0.37
	<i>g</i> -force \times concussion	-2.4×10^{-3}	-1.16	0.25
	<i>g</i> -force \times collar	8.7×10^{-5}	7.3×10^{-2}	0.94
>60 <i>g</i>	<i>g</i> -force	3.8×10^{-4}	0.50	0.62
	<i>g</i> -force \times concussion	-2.5×10^{-3}	-1.28	0.20
	<i>g</i> -force \times collar	2.8×10^{-4}	0.28	0.78
>70 <i>g</i>	<i>g</i> -force	5.4×10^{-4}	0.76	0.45
	<i>g</i> -force \times concussion	-1.9×10^{-3}	-1.08	0.28
	<i>g</i> -force \times collar	1.8×10^{-4}	0.19	0.85
>80 <i>g</i>	<i>g</i> -force	1.0×10^{-3}	1.47	0.14
	<i>g</i> -force \times concussion	-1.7×10^{-3}	-1.05	0.30
	<i>g</i> -force \times collar	-5.4×10^{-4}	-0.60	0.55
>90 <i>g</i>	<i>g</i> -force	2.0×10^{-4}	0.29	0.77
	<i>g</i> -force \times concussion	-1.4×10^{-3}	-0.86	0.39
	<i>g</i> -force \times collar	5.4×10^{-4}	0.62	0.54
>100 <i>g</i>	<i>g</i> -force	6.6×10^{-4}	0.90	0.37
	<i>g</i> -force \times concussion	-1.3×10^{-3}	-0.77	0.44
	<i>g</i> -force \times collar	-4.8×10^{-4}	-0.52	0.60
>110 <i>g</i>	<i>g</i> -force	9.3×10^{-4}	1.39	0.17
	<i>g</i> -force \times concussion	-3.9×10^{-4}	-0.24	0.81
	<i>g</i> -force \times collar	-7.6×10^{-4}	-0.88	0.38
>120 <i>g</i>	<i>g</i> -force	9.0×10^{-4}	1.45	0.15
	<i>g</i> -force \times concussion	-9.0×10^{-4}	-0.63	0.53
	<i>g</i> -force \times collar	-5.9×10^{-4}	-0.74	0.46
>130 <i>g</i>	<i>g</i> -force	5.7×10^{-4}	1.06	0.29
	<i>g</i> -force \times concussion	-4.3×10^{-4}	-0.35	0.73
	<i>g</i> -force \times collar	-1.9×10^{-4}	-0.25	0.80
>140 <i>g</i>	<i>g</i> -force	2.5×10^{-4}	0.46	0.65
	<i>g</i> -force \times concussion	-4.9×10^{-4}	-0.40	0.69
	<i>g</i> -force \times collar	-2.1×10^{-4}	-0.30	0.77
>150 <i>g</i>	<i>g</i> -force	2.6×10^{-4}	0.54	0.59
	<i>g</i> -force \times concussion	3.1×10^{-4}	0.31	0.75
	<i>g</i> -force \times collar	-2.3×10^{-4}	-0.36	0.72

^aEstimated coefficients, t-statistics and p-values are calculated with univariate linear regression
ACC=anterior cingulate cortex, tCr=total creatine + phosphocreatine creatine, tNAA=total *N*-acetylaspartate + *N*-acetylaspartyl glutamate
Significant p-values determined by $p \leq 0.05$ are bolded

Table B.10. Linear regression analysis of $\Delta_{(postseason-preseason)}/preseason$ Glx/tCr in the ACC and head impacts, concussion, and collar across all mean g-force thresholds.

g-force thresholds	Parameters	β^a	t	p
>20 g	g-force	7.8×10^{-4}	0.43	0.67
	g-force \times concussion	-4.3×10^{-3}	-1.14	0.25
	g-force \times collar	-3.3×10^{-3}	-1.25	0.21
>30 g	g-force	9.5×10^{-4}	0.76	0.45
	g-force \times concussion	-3.0×10^{-3}	-1.14	0.26
	g-force \times collar	-3.1×10^{-3}	-1.76	8.0×10^{-2}
>40 g	g-force	7.2×10^{-4}	0.72	0.47
	g-force \times concussion	-3.5×10^{-3}	-1.50	0.14
	g-force \times collar	-2.2×10^{-3}	-1.59	0.11
>50 g	g-force	4.7×10^{-4}	0.55	0.58
	g-force \times concussion	-3.1×10^{-3}	-1.57	0.12
	g-force \times collar	-1.3×10^{-3}	-1.14	0.26
>60 g	g-force	6.8×10^{-4}	0.92	0.36
	g-force \times concussion	-3.6×10^{-3}	-1.92	5.7×10^{-2}
	g-force \times collar	-1.0×10^{-3}	-1.05	0.29
>70 g	g-force	8.6×10^{-4}	1.24	0.22
	g-force \times concussion	-2.6×10^{-3}	-1.46	0.15
	g-force \times collar	-1.2×10^{-3}	-1.33	0.18
>80 g	g-force	6.8×10^{-4}	1.00	0.32
	g-force \times concussion	-1.9×10^{-3}	-1.19	0.23
	g-force \times collar	-1.0×10^{-3}	-1.17	0.24
>90 g	g-force	7.9×10^{-4}	1.18	0.24
	g-force \times concussion	-2.2×10^{-3}	-1.37	0.17
	g-force \times collar	-8.7×10^{-4}	-1.01	0.31
>100 g	g-force	1.1×10^{-3}	1.52	0.13
	g-force \times concussion	-2.6×10^{-3}	-1.56	0.12
	g-force \times collar	-9.7×10^{-4}	-1.07	0.28
>110 g	g-force	8.6×10^{-4}	1.32	0.19
	g-force \times concussion	-1.9×10^{-3}	-1.23	0.22
	g-force \times collar	-9.9×10^{-4}	-1.17	0.24
>120 g	g-force	9.5×10^{-4}	1.56	0.12
	g-force \times concussion	-1.9×10^{-3}	-1.36	0.18
	g-force \times collar	-1.1×10^{-3}	-1.40	0.16
>130 g	g-force	1.2×10^{-4}	0.22	0.82
	g-force \times concussion	-1.6×10^{-3}	-1.29	0.20
	g-force \times collar	-4.5×10^{-4}	-0.63	0.53
>140 g	g-force	-2.1×10^{-4}	-0.39	0.70
	g-force \times concussion	-1.9×10^{-3}	-1.62	0.11
	g-force \times collar	7.0×10^{-5}	0.10	0.92
>150 g	g-force	-1.8×10^{-5}	-3.8×10^{-2}	0.97
	g-force \times concussion	-1.7×10^{-3}	-1.80	7.4×10^{-2}
	g-force \times collar	1.5×10^{-4}	0.24	0.81

^aEstimated coefficients, t-statistics and p-values are calculated with univariate linear regression
ACC=anterior cingulate cortex, tCr=total creatine + phosphocreatine creatine, Glx=glutamine + glutamate
Significant p-values determined by $p \leq 0.05$ are bolded

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