EVALUATION OF TIME-WEIGHTED CUMULATIVE HEAD IMPACT EXPOSURE METRICS ON DIFFUSION-BASED IMAGING METRICS IN YOUTH FOOTBALL

BY

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LIST OF ABBREVIATIONS

C_L	Linear Anisotropy
C_P	Planar Anisotropy
C_S	Spherical Anisotropy
CTE	Chronic Traumatic Encephalopathy
DTI	Diffusor Tensor Imaging
FA	Fractional Anisotropy
FE	Finite Element
HIE	Head Impact Exposure
HIT	Head Impact Telemetry
MD	Mean Diffusivity
MRI	Magnetic Resonance Imaging
mTBI	Mild Traumatic Brain Injury
NCAA	National Collegiate Athletic Association
RWE	Risk-Weighted Exposure
TBH	Time Between Hits
TUA	Time Until Assessment
TWE	Time-Weighted Exposure

ABSTRACT

Head impacts sustained in football represent one of the largest sources of head injury and subconcussive head impact exposure (HIE) in the United States, and their effects on the brain can be devastating in the short and long term. Current efforts to understand the effects of HIE on the brain include the development of cumulative HIE metrics to assess an athlete's exposure to head impacts over a season. Existing metrics incorporate the volume (i.e., number) and magnitude (i.e., severity) of impacts experienced by an athlete, and have been shown to be associated with structural changes in the brain observed after a single season. Another variable which has been less commonly considered is time. Incorporating time of impacts in relation to other relevant events into cumulative HIE metrics may lead to improved understanding of the effects of repeated subconcussive HIE on the brain.

In the first part of this thesis, metrics of cumulative HIE that consider the volume, magnitude, and timing of impacts are evaluated with respect to total changes in diffusion-based MRI metrics. In the second part, the relationship between time-weighted cumulative HIE metrics and directional changes in diffusion-based MRI metrics is evaluated. The overall goal of this research is to evaluate the value in using time-weighted cumulative HIE metrics to understand the effects subconcussive HIE on changes in the brain after a single season.

CHAPTER I: INTRODUCTION

It is estimated that between 1.6 million and 3.8 million concussions are attributable to sports and recreation occur every year.[1] Concussion is a neurological condition commonly associated with biomechanical injury to the head. Short-term symptoms of concussion include confusion, memory loss, disorientation, loss of balance, headaches, visual disturbances, and loss of consciousness.[2] These symptoms may resolve completely over time, with observable symptoms, diagnostic measures, and blood biomarkers that indicate concussion diminishing over the course of around 7 days.[3–5] However, the long-term effects of a single concussion or even a series of repeated subconcussive impacts can manifest in conditions such as chronic traumatic encephalopathy (CTE) or others that feature chronic neurological deficits.[6–9] Among contact sports, football has one of the highest incidence rates of concussion.[10–12] Approximately 70% of football athletes are under the age of 18, comprising around 3.5 million individuals.[13] Accordingly, the epidemiology of concussive and subconcussive head impact exposure (HIE) in youth athletes is an important area of study.

To understand the effects of repeated head impacts on negative neurological sequelae, cumulative HIE metrics have been developed. To obtain the biomechanical data needed to develop and study cumulative HIE metrics, multiple technologies exist to measure the linear and rotational acceleration of the head resulting from head impacts. One common technology used in the research community is the Head Impact Telemetry (HIT) System.[14] This system involves outfitting football helmets with 6-accelerometer arrays (MxEncoder). These instrument-equipped helmets are provided to enrolled athletes allowing for the monitoring of head impacts using an observational method (i.e., as they

would occur during normal participation in the sport), thus collecting data on potentially harmful events without the active inducement of those events.

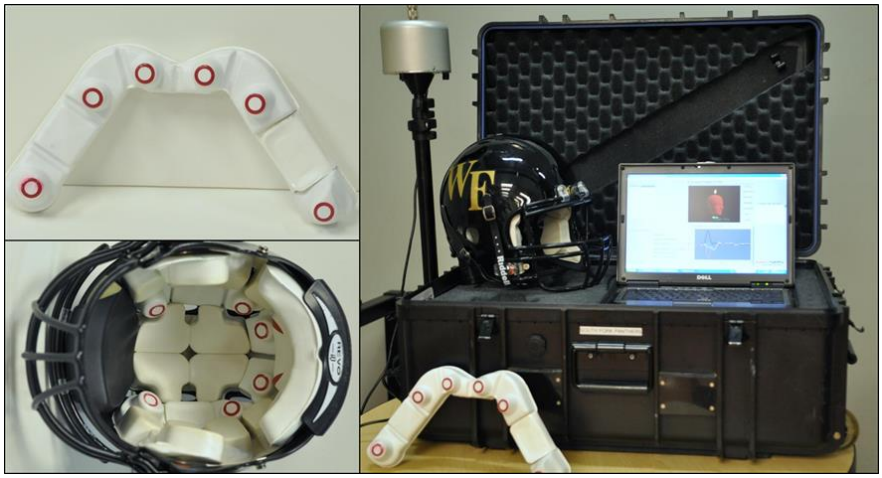

Figure 1. Head Impact Telemetry (HIT) System. (Top Left) MxEncoder, (Bottom Left) MxEncoder fit within the padding of the helmet, (Right) Sideline controller.

Cumulative HIE metrics are often evaluated with respect to clinical outcome measures to understand changes in the brain that may occur after exposure to repeated head impacts. One common clinical outcome measure is diffusion-tensor imaging (DTI), which is an MRI sequence that is more capable of detecting changes in the brain connected with this kind of injury than conventional structural MRI.[15–17] DTI metrics detect the change of flow of water molecules in the brain. These changes often occur as a result of microscopic alterations in the structure and arrangement of tissue as a result of injury. Previous studies have demonstrated an association between cumulative HIE and diffusion-based MRI metrics.[18–20]

Cumulative HIE metrics quantify a player's exposure to head impacts by considering the number of head impacts as well as the peak resultant linear and/or rotational acceleration experienced during each head impact. Urban et al. developed a cumulative HIE metric that takes the impacts' accelerations into account to calculate the

estimated risk of concussion associated with each impact and summing the individual risks to calculate a single number representing the athlete's cumulative HIE over the entire season of play known as risk-weighted exposure (RWE).[13] The basis for RWE is concussion injury risk derived from equations developed by Rowson et al to non-linearly weight the magnitude of each impact based on how it will contribute to overall chance of injury.[21] Initially, the concussion risk equations individually considered the linear and rotational acceleration of the event. However, because both linear and rotational acceleration are likely to contribute to injury through different mechanisms, Rowson et al. created a concussion risk equation called the combined probability of concussion that incorporates both. When incorporating the combined probability of concussion as a measure of concussion risk in RWE, the volume of impacts, as well as the combined linear and rotational magnitude of each impact is considered. While this version of RWE is a robust measure of cumulative HIE, it does not consider factors such as when impacts occur relative to one another, an important element to brain recovery from head impacts.

In the following chapters, I will discuss my efforts to develop novel, improved cumulative HIE metrics to investigate ways to better understand the effects of subconcussive HIE on the brain. Prior metrics, such as RWE, encompass volume and magnitude of head impacts. I expand upon existing cumulative HIE metrics by adding an important variable of HIE: time. The time between impacts is considered and used to weight the magnitude of head impacts using various scaling methods; additionally a metric that considers when impacts occur relative to the athlete's post-season assessment is evaluated. Each metric is evaluated with respect to abnormal changes in diffusion-based MRI metrics. Total changes in the brain, as well as directional changes (corresponding with

different effects in the brain, such as acute and chronic phases of injury separately) were assessed to gain a better understanding of the mechanisms of changes observed in the brain.

Chapter Summaries

Chapter II: Using Time-Weighted Metrics to Interpret White Matter Changes from Cumulative Head Impact Exposure in Youth Football

The objective of this study was to develop time-weighted cumulative head impact exposure metrics and compare them with total changes in abnormal voxels of diffusion-based MRI metrics. This research was conducted using a dataset collected from a sample of players outfitted with the HIT system. Time-weighted metrics were compared with non-time-weighted metrics to determine the benefit of including time as a variable in cumulative HIE metrics.

Chapter III: The Effects of Time-weighted Cumulative Head Impact Exposure Metrics on Directional Changes in Diffusion Imaging

The objective of this study was to compare time-weighted cumulative head impact exposure metrics with directional changes in diffusion-based MRI metrics in order to determine specific relationships between biomechanical metrics and acute and chronic phases of injury specifically. This research was also conducted using data collected from players outfitted with the HIT system.

Chapter IV: Summary of Research

A summation of the research discussed in this thesis.

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CHAPTER II: USING TIME-WEIGHTED METRICS TO INTERPRET WHITE MATTER CHANGES FROM CUMULATIVE HEAD IMPACT EXPOSURE IN YOUTH FOOTBALL

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Structured Abstract

Objective: Nearly 5 million athletes play football in the US. Repeated head impacts received while playing football may result in long-term neurodegeneration, with subtle microstructural and functional changes occurring after a single season. Existing cumulative head impact exposure (HIE) metrics only account for the number and/or magnitude of impacts without considering the relative frequency of each impact. The objective of this study was to investigate the effect of time between successive head impacts on changes in diffusion tensor imaging (DTI) measures in a sample of youth football players.

Methods: Youth football players (n=95) were instrumented with helmets fitted with the Head Impact Telemetry (HIT) System during practices and games. Three cumulative time-weighted HIE metrics were evaluated: time-weighted exposure (TWE) with exponential time-weighting ($TWE_{Exponential}$), TWE with inverse time-weighting ($TWE_{Inverse}$), and time-weighted exposure relative to the time until assessment (TUA). In addition, the number of impacts and risk weighted exposure (RWE) were calculated. Each HIE metric was linearly regressed with number of abnormal DTI voxels from each participant.

Results: On average, number of impacts (mean R^2=0.2567) was most strongly correlated with DTI metrics, followed closely by log $TWE_{Exponential}$ (mean R^2=0.2263), log TUA (mean R^2 = 0.2152), log $TWE_{Inverse}$ (mean R^2=0.1791), and RWE (mean R^2=0.1619).

Conclusions: The results suggest value in incorporating time as a variable in the investigation of the effects repeated subconcussive HIE.

Introduction: Football is among the contact and collision sports with the highest incidence of concussion.[1–3] There are over five million football-playing athletes in the United States alone. A significant majority of these players are in youth and high school leagues, meaning a majority of football players are children and adolescents.[4–6] Numerous past efforts have focused on studying the long-term effects of repeated head impacts in adult athletes.[7] There is a growing body of literature describing research related to short-term, or single-season changes in the brain among younger players.[5,6,8] Considering the high proportion of youth athletes in football, there is value in studying the effects of repeated head impacts in this population.

Repeated head impact exposure (HIE) may lead to long-term neurological deficits and neurodegeneration,[9,10] and may result in short-term changes in the brain after a single season.[11–13] These findings have motivated the development of methods to quantify cumulative HIE. Davenport et al. studied the relationship between cumulative HIE and measurable changes in MRI metrics.[14] A cumulative exposure metric called risk-weighted exposure (RWE) was calculated for a sample of high school athletes and compared with values of diffusion-based MRI metrics. Results of this study demonstrated that RWE was more strongly correlated with changes in MRI metrics than simple summation of impacts (i.e., number of impacts) and indicated RWE is a viable metric to understand the relationship between repeated HIE and single-season changes in the brain.

There is another dimension of cumulative HIE that deserves consideration for its relevance in brain healing: time. Broglio et al. evaluated differences in HIE among concussed and

non-concussed (i.e., control) football players to evaluate the effect of impact density (i.e., temporal proximity of head impacts) on concussion risk. In this approach, the linear and rotational acceleration of each concussive head impact event (or comparable event for the control athlete) were scaled separately by inverse time between events and summed over impacts leading up to the concussive event. Using this time-weighted approach, they found concussed players had higher linear and rotational impact density than non-concussed counterparts.[15] They concluded time between impacts, along with magnitude, influences concussion risk. Merchant-Borna et al. also studied approaches to weighting cumulative HIE by time in a sample of high school football players but applied this theory to the study of subconcussive HIE.[16] Merchant-Borna evaluated the compounding effect of both time between hits and the time until assessment (the hypothesis being that impacts become less prominent, or have less effect on the brain, as time passes). Results of this prior study demonstrated a stronger correlation between cumulative exposure and white matter changes when exposures were weighted by time.

Previous work has demonstrated the benefits of implementing time-weighting approaches to quantify cumulative HIE, but this approach has not been applied to youth populations, and few studies have incorporated exposure measurements combining both linear and rotational acceleration components. Therefore, this study will further explore the effect of time by employing an alternative approach to time-weighting and considering both linear and rotational acceleration in the measure of exposure. The objective of this study is to investigate the effect of time when evaluating the relationship between cumulative HIE on diffusion-based imaging metrics in a sample of youth athletes.

Methods: Youth football players were enrolled for participation in this study approved by the Wake Forest School of Medicine Institutional Review Board. All participants were members of one of three youth football leagues in Winston-Salem, NC. Each participant was provided a Riddell Speed or Revolution football helmet fitted with a Head Impact Telemetry (HIT) System MxEncoder, a 6-sensor accelerometer array that records and stores head impacts received by the player in real-time.[17] Each football practice and game was attended by a researcher who operated the HIT System and filmed the event using a time-synchronized camera. Post-season, each film was reviewed to ensure head impacts registered were not erroneous. Data was collected over the course of 6 seasons from 2012-2017. Methods for data processing have been previously described.[18,19] Non-contact athletes participating in tennis, basketball, baseball, and karate were recruited as a control sample from club and school-based programs in Winston-Salem, NC. Control participants were screened to ensure they had no history of concussion or suspected concussion while participating in the study. They were further screened to ensure no active or prior participation in contact sports. Participants were excluded if they had prior brain surgery, traumatic brain injury, or did not wear helmets compatible with the HIT system.

Each football player completed an MRI with a 3 Tesla Siemens Skyra MRI scanner prior to the start of the season and after the completion of the season. Control participants also completed MRI scans at baseline and at a follow-up 89-180 days later. MRI scans were visually evaluated for structural abnormalities and motion artifact by a board certified neuroradiologist. Subjects with clinically relevant abnormalities (such as tumors, or an unreasonably high white matter lesion load for their age) or motion artifact were excluded

from analysis. MRI acquisition and processing has been previously described in Davenport et al.[14] T1-weighted images as well as diffusion kurtosis imaging (DKI) were acquired as part of the pre-season and post-season MRI scans. DKI was pre-processed using FSL and eddy current correction. Voxel-wise DTI scalar metrics: fractional anisotropy (FA), mean diffusivity (MD), linear anisotropy (CL), planar anisotropy (CP), and spherical anisotropy (CS), were computed from the DKI images using DTI-TK. These scalar maps were then warped to Montreal Neurologic Imaging (MNI) space based on the SPM8 normalization from the T1 image. The initial DKI protocol (for 2012-2013 seasons) parameters included a 10500ms/99ms TR/TE, 90° flip angle, and a 2.2x2.2x3.0mm voxel resolution, while the subsequent DKI protocol (for 2014-2017 seasons) parameters included a 12600ms/100ms TR/TE, 90° flip angle, and a 2.0x2.0x2.0mm voxel resolution. Both DKI protocols included b-values of 0, 1000, and 2000. Each pre-season DTI-metric scalar map was then subtracted from the post-season map for each player, creating a delta map for each metric. The same was done for control subjects, subtracting the baseline scalar maps from the follow-up maps. The voxel-wise group mean and standard deviation of the controls' delta maps were used to calculate voxel-wise z-scores for each football player.

Abnormal voxels were identified by thresholding the z-maps at 2 standard deviations (SD) above the mean or 2 SD below the mean. This identified both abnormally high and low scalar values, respectively. A cluster threshold requiring a minimum 1 mL contiguous volume was applied to reduce false positives. The total number of abnormally increasing (above 2 SD), abnormally decreasing (below -2 SD) voxels, and the total number of abnormal voxels (sum of each) for each subject and scalar metric was computed.

Biomechanical Metrics: Several biomechanical metrics were investigated with respect to changes in pre- to post-season DTI metrics, including number of impacts, RWE, and three time-weighted cumulative exposure metrics: exponential time-weighted exposure (TWEExponential), inverse time-weighted exposure (TWEInverse), and time until assessment (TUA) (Table 1). Number of impacts is the total number of impacts recorded over the course of the season for each athlete. This metric does not consider the magnitude of the impact or the time it occurred. RWE is a method which combines the magnitude and frequency of hits experienced by an athlete by non-linearly weighting each impact by the estimated concussion risk. To compute RWE, the risk of concussion of each impact for each player in a season was calculated using the combined probability risk function (CP) previously described by Rowson and Duma and summed.[20] The logistic regression equation is provided in Table 1, where $\beta 0$ is -10.2, $\beta 1$ is 0.0433, $\beta 2$ is 0.000873, $\beta 3$ is -9.2E-7 and a_i and α_i are the peak resultant linear and rotational acceleration, respectively, for each impact.

Table 1. Biomechanical Exposure Metrics (All metrics are unitless, representing injury risk)

Abbreviation	Description	Equation
X	Combined Probability injury risk function	$\left(\frac{1}{1+e^{-(\beta 0+\beta 1 a_i+\beta 2\alpha_i+\beta 3 a_i\alpha_i)}}\right)$
RWE	Risk-Weighted Exposure	$\sum_{i=1}^{n} X_C$
$TWE_{Exponential}$	Exponential Time-Weighted Exposure	$\sum_{i=1}^{n}\left[X_c+\sum_{j=1}^{m}\left[\left(e^{\gamma(T_c-T_p)}\right)*X_p\right]\right]$
$TWE_{Inverse}$	Inverse Time-Weighted Exposure	$\sum_{i=1}^{n}\left[X_c+\sum_{j=1}^{m}\left[\left(\frac{b}{T_c-T_p}\right)*X_p\right]\right]$
TUA	Time Until Assessment	$\sum_{i=1}^{n}\left[\left(\frac{b}{T_D-T_c}\right)*X_c\right]$

The equation for each time-weighted metric is provided in Table 1 and described below. 'X_C' represents the magnitude of a given (i.e., current) impact, 'X_P' represents the magnitude of an impact that occurred before the impact under consideration (i.e., prior to). 'n' is the total number of impacts the player experienced, 'm' is the number of impacts that occurred in a preceding time window, where the duration of the time window under consideration is defined by the metric. 'T_c' is the time of the current impact, 'T_p' is the time of a prior impact. The remaining variables specific to each time-weighted metric are further described below.

To account for the combined effect of linear and rotational acceleration experienced in each impact and to create a time-weighted exposure metric comparable to RWE, the combined probability of each impact was calculated and used as the measure of exposure in each time-weighted exposure metric – $TWE_{Exponential}$, $TWE_{Inverse}$, TUA. Additionally, for each

time weighted metric, time was measured in units of hours. Each metric is unitless (except for number of impacts, which is a count), representing injury risk. Each time-weighted metric is described in detail below.

Exponential Time-Weighted Exposure ($TWE_{Exponential}$): For a given impact (X_C), each prior impact (X_P) within a specified time window was weighted based on an exponential decay function ranging from 0 to 1, as a function of time between the given impact and the prior impact. An exponential decay constant ($\boldsymbol{\gamma}$ = -0.3) was multiplied with the time interval (i.e., the time between the current impact and the prior impact) in the exponent (T_c–T_p). A range of exponential decay constants were tested (-0.1 to -0.5), with little change in the calculated value among constants lower than -0.3. As a result, -0.3 was chosen as the exponential decay constant for this metric. A time window of 72 hours was chosen based on literature that indicates this to be the approximate timeframe for blood biomarkers associated with traumatic brain injuries to return to normal levels, suggesting recovery from a concussive head impact.[21–23] For each head impact, the exponential time-weight was applied to all head impacts occurring 72 hours prior to the given head impact. This was iteratively computed for every head impact over the course of season and summed to generate a single value representing the cumulative exponentially time-weighted exposure.

Inverse Time-Weighted Exposure ($TWE_{Inverse}$): This method was derived from the work of Merchant-Borna et al, except it uses CP as the exposure metric instead of peak acceleration values.[16] For a given impact (X_C), only impacts that occur on the same day are considered. The time-weighting scale factor used in this method weights each impact

inversely by the time between the given (i.e., current) impact and every previous impact that occurred the same day. In this equation, the time difference (T_c–T_p) is between the current and prior impacts respectively, and 'b' represents a constant that has a value of 1 hour.

Time Until Assessment (TUA): This method was also derived from Merchant-Borna et al, but uses CP as the measure of exposure instead of peak acceleration values.[16] In this approach, impacts are evaluated relative to the post-season assessment. The CP of each impact is multiplied with the inverse of the time difference between the time of post-season assessment (T_D) and the time of impact (T_c). As a result, impacts closer to the end of the season are weighted more heavily than those that occurred near the beginning of the season. In this equation, the time difference (T_D–T_c) is between the time of post season scan and the given impact respectively, and 'b' represents a constant that has a value of 1 hour.

In Table 2, the different components included in the metrics used in this study are shown.

Table 2. Biomechanical Metrics and their inclusion of frequency of impacts, magnitude of impacts, and time at which the impacts occurred

Metric	Frequency	Magnitude	Time
Number of impacts	✓		
RWE	✓	✓	
$TWE_{Exponential}$	✓	✓	✓
$TWE_{Inverse}$	✓	✓	✓
TUA	✓	✓	✓

Statistical Analysis: The relationship between each biomechanical metric and the logarithmic transformation of the number of abnormal DTI voxels for each subject was

evaluated using linear regression. Primary analysis was between biomechanical metrics and total abnormal voxels derived from DTI metrics (FA, MD, CL, CP, and CS). Time-weighted biomechanical metrics were logarithmically transformed before linear regression to account for skewness in the distributions of these metrics. Also, collinearity of predictor variables was evaluated to ensure that the predictor variables (i.e., biomechanical metrics) were not highly associated. Cook's distance was calculated using 4/n, where n is the total number of participants, and outliers were removed from the final dataset for each regression. Additionally, covariate adjustment was conducted to improve fit, accounting for differences in age, weight, time between scans, and difference in imaging protocol between seasons. Statistical analysis was completed in SAS v.9.4 (Cary, NC).

Results: In total, 95 youth athletes enrolled in this study participated in at least one of six seasons of play and had complete and high-quality MRI data, resulting in 117 player-seasons. The average age and weight of the participants was 11.9±1.0 years and 110.6±21.4 lbs, respectively. Over the course of six years of data collection, 34,039 verified impacts were recorded from this sample of athletes, with an average (± standard deviation) number of impacts per player per season of 290.9±205.8. Summary statistics of biomechanical metrics calculated in this study are provided in Table 3. Eleven control participants were enrolled in the study who played sports including tennis, baseball, basketball, and karate. Their average age and BMI were 11.0±2.0 years and 18.6±2.3 respectively. They were all scanned pre-season and post-season, with an average time between scans of 119.3±32.0 days.

Table 3. Summary Statistics of Biomechanical Metrics

Metric	Mean (± Standard Deviation)	Median	95th Percentile	Skewness Coefficient	Coefficient of Variation
Number of impacts	290.9 ± 205.8	222	681.8	0.999	0.707
RWE	0.44 ± 0.58	0.18	1.76	2.056	1.318
$TWE_{Exponential}$	4.87 ± 9.39	1.35	22.13	3.678	1.928
$TWE_{Inverse}$	1088 ± 1855	374	5718	2.593	1.705
TUA	$4.16 \times 10^{-4} \pm 8.97 \times 10^{-4}$	1.85×10^{-4}	1.90×10^{-4}	6.726	2.156

Evaluating collinearity of predictor variables, number of impacts and RWE were weakly correlated (R^2=0.41) but only slightly less correlated than number of impacts and $TWE_{Exponential}$ (R^2=0.49). RWE and $TWE_{Exponential}$ were more strongly correlated (R^2=0.75) but $TWE_{Exponential}$ still provided unique information within each measure. It is important to note that RWE, $TWE_{Exponential}$, $TWE_{Inverse}$, and TUA are all unitless metrics representing quantification of injury risk. They sometimes use widely varying time scales, explaining the order of magnitude variation in the final results. Values should not necessarily be compared to each other; the goal was to examine the ability of the metrics to explain variance in imaging results. The time distribution of a single player's impacts over the course of a season, as well as over the course of a single day are provided in Figure 2. In the upper plot, each dot represents a cluster of impacts that occurred in a single day and are themselves distributed as in the lower plot (where each dot represents an impact, or a cluster of impacts occurring over the course of a few minutes), The large gaps that occur between impacts constitute the basis for the hypothesized benefit of time-weighted cumulative HIE metrics.

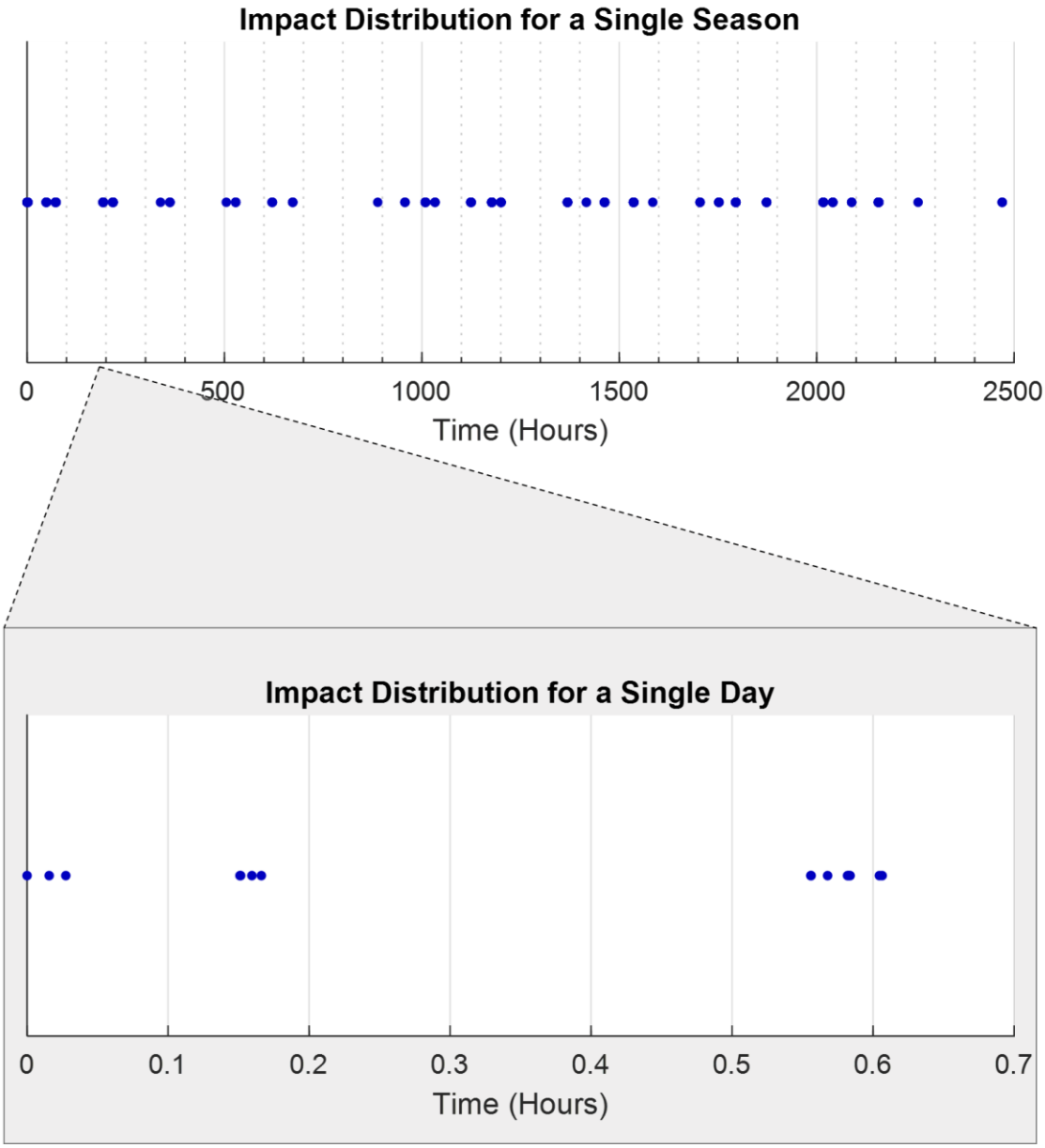

Figure 2. Distribution of Impacts for a single player over course of a single season (293 impacts) and single session (15 impacts)

The skewness coefficient of each metric, in addition to visual examination of the distributions, was used to determine the necessity of log-transforming the biomechanical metrics before performing linear regressions. Using the Fisher-Pearson standardized moment coefficient of skewness, $TWE_{Exponential}$, $TWE_{Inverse}$, and TUA were observed to be highly right-skewed with skewness values much greater than 2, and were, thus, log-transformed.[24]

Table 4 shows the results of the linear regression analyses between biomechanical metrics and total abnormal voxels. All comparisons were statistically significant ($p<0.05$). Evaluating the relationship between log FA voxels and biomechanical metrics, number of impacts was most strongly correlated ($R^2=0.2767$), followed by log $TWE_{Exponential}$ ($R^2=0.2624$) and log TUA ($R^2=0.2347$). For DTI metric sub-measures (C_L, C_S, C_P), number of impacts remained the most strongly correlated, but time-weighted metrics consistently had stronger relationships with DTI metrics than the non-time-weighted metric RWE. Figure 3 shows the positive linear relationship between log FA voxels and number of impacts, RWE, log $TWE_{Exponential}$, log $TWE_{Inverse}$, and log TUA. Looking at the average across DTI measures, number of impacts (mean $R^2=0.2567$) was most strongly correlated with DTI metrics, followed closely by log $TWE_{Exponential}$ (mean $R^2=0.2263$), log TUA (mean $R^2=0.2152$), log $TWE_{Inverse}$ (mean $R^2=0.1791$), and RWE (mean $R^2=0.1619$).

Table 4. Linear Regression Analysis of Biomechanical Metrics and DTI Metrics (* represents statistically significant relationships $p<0.05$). All imaging metrics and time-weighted metrics ($TWE_{Exponential}$, $TWE_{Inverse}$, and TUA) were log transformed.

Comparisons	Total Abnormal Voxels		
	Covariate Adjustment for age, weight, time between scans and imaging protocol		
	Adjusted R^2	p value	Adjusted R^2 Rank
FA vs. # Impacts	**0.2767**	**<0.0001***	**1**
FA vs. RWE	**0.1787**	**0.0001***	**5**
FA vs. $TWE_{Exponential}$	**0.2624**	**<0.0001***	**2**
FA vs. $TWE_{Inverse}$	**0.1982**	**<0.0001***	**4**
FA vs. TUA	**0.2347**	**<0.0001***	**3**
MD vs. # Impacts	**0.1379**	**0.0008***	**4**
MD vs. RWE	**0.1205**	**0.0024***	**5**
MD vs. $TWE_{Exponential}$	**0.1518**	**0.0005***	**2**
MD vs. $TWE_{Inverse}$	**0.1510**	**0.0005***	**3**
MD vs. TUA	**0.1737**	**0.0001***	**1**
C_L vs. # Impacts	**0.2856**	**<0.0001***	**1**
C_L vs. RWE	**0.1464**	**0.0006***	**4**
C_L vs. $TWE_{Exponential}$	**0.2467**	**<0.0001***	**2**
C_L vs. $TWE_{Inverse}$	**0.1385**	**0.0009***	**5**
C_L vs. TUA	**0.2207**	**<0.0001***	**3**
C_S vs. # Impacts	**0.2509**	**<0.0001***	**1**
C_S vs. RWE	**0.1512**	**0.0005***	**5**
C_S vs. $TWE_{Exponential}$	**0.1963**	**<0.0001***	**2**
C_S vs. $TWE_{Inverse}$	**0.1680**	**0.0002***	**4**
C_S vs. TUA	**0.1878**	**<0.0001***	**3**
C_P vs. # Impacts	**0.3323**	**<0.0001***	**1**
C_P vs. RWE	**0.2126**	**<0.0001***	**5**
C_P vs. $TWE_{Exponential}$	**0.2740**	**<0.0001***	**2**
C_P vs. $TWE_{Inverse}$	**0.2397**	**<0.0001***	**4**
C_P vs. TUA	**0.2588**	**<0.0001***	**3**

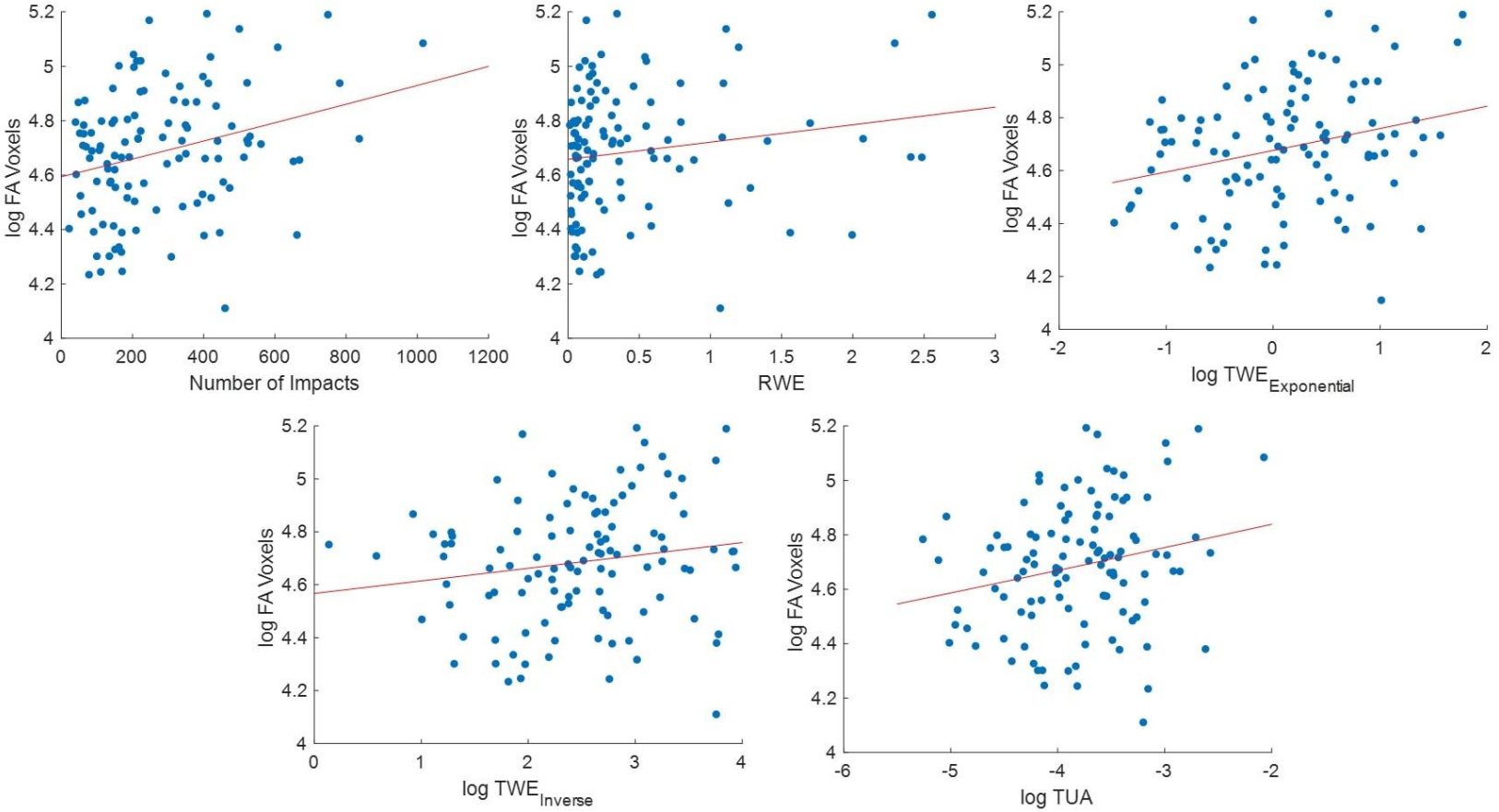

Figure 3. Linear regression between number of impacts, RWE, $TWE_{Exponential}$, $TWE_{Inverse}$, and TUA, and total abnormal FA voxels for all impacts

Discussion: The objective of this study was to investigate the relationship between cumulative HIE and changes in DTI metrics in a sample of youth football players and evaluate the effect of time-weighting on this association. This study focused on youth athletes, a large segment of athletes for whom little is known about the effects of cumulative HIE on the brain.[25,26] The findings of this study indicate that time-weighting approaches typically yield stronger associations with DTI metrics than non-time-weighted approaches.

RWE is a metric previously demonstrated to have value for understanding the effect of cumulative HIE on changes in the brain in the absence of concussion.[11,14,27,28] In this study, we expanded on the risk-weighted approach by applying time-weighting to the calculation of cumulative exposure. In general, the results of this study demonstrate that time-weighted exposure is more strongly correlated with abnormal DTI voxels than solely risk-based measures like RWE. This is consistent with other studies that have looked into time-weighted exposure, which also identify correlations between HIE and changes in the brain.[15,16] In particular, $TWE_{Exponential}$, a metric where impact events are weighted by an exponential decay function for time between impacts, was more strongly correlated with imaging metrics than RWE. This indicates that the timing of impacts relative to one another is an important consideration when evaluating the effects of cumulative HIE on brain changes. This may be because the brain requires a period of time to recover after receiving an impact, and during this recovery period it is more susceptible to injury. However, there is limited existing literature demonstrating the brain's recovery time following subconcussive head impacts and cumulative HIE. Knowledge of how quickly the brain

recovers from such events is critical in developing a robust time-weighted HIE metric.[21–23]

The total number of impacts is a cumulative exposure metric that does not account for the magnitude of each impact. Among comparisons with DTI metrics and biomechanical metrics, number of impacts had the strongest relationships with all DTI metrics except MD. One explanation for this is that the youth population studied has a narrower distribution of impact magnitudes, and a population with greater variance in magnitudes could benefit more from time-weighted metrics. The volume of impacts an athlete receives may contribute significantly to changes in the brain. In the study by Broglio et al, concussed players sustained more impacts than non-concussed players in a 24 hour testing period.[15] These results support efforts to reduce exposure in youth football to reduce detrimental effects on the brain. Various organizations have implemented exposure-reducing policies by limiting contact practices, including the National Collegiate Athletic Association (NCAA) and Pop Warner Football, and some researchers have investigated the benefits of reducing contact,[29,30] but the effect of these policy changes on reducing brain changes has not been investigated.

Merchant-Borna et al. found that cumulative HIE weighed inversely with time correlated with white matter changes in the brain. In this study, we adapted the equations developed by Merchant-Borna et al. by using CP (i.e., risk derived from peak linear and rotational acceleration of an impact) as the measure of exposure, as opposed to peak resultant linear or rotational acceleration alone. Log $TWE_{Exponential}$ consistently had stronger associations with DTI metrics compared to log $TWE_{Inverse}$ and log TUA, although log TUA had a stronger relationship in two comparisons (log FA and log MD). This suggests that

exponential decay with time of exposure may be a superior method of time-weighting than inverse scaling and that the time of post-season scan is important. This may be because $TWE_{Inverse}$ only includes impacts from the most recent day, rather than the 72-hour time window used in $TWE_{Exponential}$. This time frame is longer than that used in previous studies, and aligned with the estimated recovery time of the brain following concussion, as well as the rate of decline on injury.[21–23] This would be expected to yield stronger relationships, but the results indicate otherwise. It is possible that the clinical outcome measures in the present study are calculated slightly differently from the past studies, these methods may not be as effective for youth populations, or the larger sample size of this study resulted lower correlations. In this paper, a voxel was considered abnormal if its value was at least two standard deviations higher or lower than the control group whereas Merchant Borna et al. determined abnormality using a non-parametric bootstrap technique. Different time windows can be employed to consider different rates of brain recovery or different hypotheses about the brain's sensitivity to temporal (time) proximity of subconcussive impacts. Time-weighted metrics may be employed among athletes at a different levels of play to assess whether age is a factor in the efficacy of the current approach. Future work could involve refining the cumulative exposure metrics to incorporate youth-specific risk functions[31] as well as modifying the methodology in DTI metric and/or time weighting metrics to improve correlation between biomechanical metrics and clinical outcome metrics.

The exposure component of each biomechanical metric investigated in this study was CP, a non-linear measure of risk. Previous cumulative time-weighted exposure metrics have only considered peak resultant linear or rotational acceleration, but each head impact is

comprised of both linear and rotational motion and the combined effect may be important to understand impact exposure of the brain. TUA was consistently one of the biomechanical metrics that was more strongly correlated with MRI metrics in the present study, similar to Merchant Borna et al (Merchant-Borna et al. TUA mean R^2=0.40, as compared to our TUA mean R^2=0.22). The difference may be due to several factors such as the age of the population (youth vs. collegiate), different sample sizes (117 player seasons vs. 10), different time windows (72 hours vs. same day), and methods of analysis (exponential vs. inverse time scaling and variations in DTI calculation).[25,26] However, the advantage to incorporating time of post-season testing into a risk metric is evident. It seems that the proximity of time of impacts to the time of post-season assessment plays a role in injury that needs to be better understood.

While the results of this study provide insight into the effect of time-weighted HIE on pre- to post-season DTI metrics, there are some limitations that must be acknowledged. First, while significant relationships were observed among most of the comparisons in this study, the strength of the associations were relatively low (R^2<0.22) for all comparisons listed. One possible explanation for this is that a great number of factors affect the physiology of a young person's brain, and voxel-based changes observed may be due to a myriad of individual, personal considerations. For instance, factors such as diet, stress, health, etc. that are not related to their experiences on the football field, making high R^2 values unlikely. Additionally, the accuracy of the HIT system that was used to collect acceleration data must be considered. Multiple previous studies have made use of this system and have found it to be accurate and reflective of the actual HIE received by the athletes.[32] Lastly,

the brain's response to injury is not fully understood, and this knowledge is important when accurately predicting injury risk.

The biomechanical response of the brain to impacts is directionally dependent. A recent study by Asselin et al. investigated the effects of using cumulative time-weighted exposure metrics on white matter changes in the brain using a region-specific algorithm called SPREAD[33] and demonstrated significant relationships between cumulative exposure metrics and region-specific white matter changes. Finite element (FE) modeling and strain-based metrics characterize volumetric and regional brain response to impacts, and account for the directionally-dependent response of the brain.[34] Future efforts should be made to incorporate region of interest (ROI)-based approaches integrating brain FE models and MRI data to further study the effects of repeated HIE on the brain.

Conclusion: The objective of the study was to examine the relationship between cumulative HIE and changes in diffusion-based imaging metrics in a sample of youth football players and assess the effect of time-weighting cumulative HIE on this relationship. The findings of this study demonstrate that time-weighted measures tended to have stronger associations with MRI metrics than non-time-weighted measures such as RWE. The results of this study suggest value in incorporating time as a variable in the investigation of the effects of repeated subconcussive HIE. Future work will include FE modeling of impacts for ROI- and strain-based assessment of the effects of repeated HIE on the brain as well as investigating the ability of time-weighted metrics to predict solely acute or chronic changes in the brain.

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CHAPTER III: THE EFFECTS OF TIME-WEIGHTED CUMULATIVE HEAD IMPACT EXPOSURE METRICS ON DIRECTIONAL CHANGES IN DIFFUSION IMAGING

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Abstract

Approximately 5 million youth and adolescents in the US play football, a sport with one of the highest rates of concussion. Repeated subconcussive head impact exposure (HIE) may lead to negative neurological sequelae. In order to understand the effect of HIE on brain changes, quantitative cumulative HIE metrics have been developed that capture the volume (i.e., number), magnitude (i.e., severity), and/or time at which head impacts occur (i.e., frequency). In this study, cumulative HIE metrics were compared with directional changes in DTI metrics to determine relationship between cumulative HIE on directionally-associated changes in the brain. Cumulative HIE metrics were more strongly correlated with increases in abnormal voxels than decreases in abnormal voxels. Additionally, across DTI sub-measures, increases and decreases in mean diffusivity (MD) had the strongest relationships with HIE metrics (increases in MD: average $R^2 = 0.1753$, average $p = 0.0002$; decreases in MD: average $R^2 = 0.0997$, average $p = 0.0073$). This encourages further investigation into the physiological phenomena represented by directional changes.

Introduction

Football is a sport with a high incidence of concussion.[1-3] Of the approximately 5 million football-playing athletes in the US, a majority of them play at the youth and high school level and, thus, there are a significant number of children and adolescent athletes who experience a large amount of subconcussive head impact exposure (HIE).[4-6] Studies have shown that repeated subconcussive HIE can lead to neurotrauma, and a greater accumulation of damage can occur if HIE is prolonged, particularly in youth players.[7-9] As such, there is increasing interest in studying the effect of repeated HIE in this age group.

Efforts to create quantitative measures of cumulative HIE arose from neurological deficits observed in athletes after they received repeated head impacts.[9-10] Some studies conducted to measure these deficits have identified short-term changes after a single season of play.[7-11] These measures take into account the volume and magnitude of impacts sustained by players, and some recent studies have also taken into account the timing between impacts (time-weighting).[12-13] Time-weighting incorporates additional information (such as the brain's capacity to recover from head impacts) into HIE measures. The efficacy of HIE metrics in evaluated changes in the brain are often assessed by investigating their relationship with changes pre- to post-season clinical outcome measures thought to be correlated with injury. Conventional MRI has been used to identify non-specific abnormalities following sports-related concussions. However, such modalities have been reported to lack the utility in diagnosing or describing certain specific changes to tissues.[14] Alternatively, studies have employed diffusion tensor imaging (DTI), which offers in vivo measures of molecular water diffusion in the brain.[15-18] Accordingly, DTI metrics like fractional anisotropy (FA), mean diffusivity (MD), linear anisotropy (C_L), spherical anisotropy (C_S), and planar anisotropy (C_P) can be used to interrogate specific brain microstructural changes associated with mTBI.[19] The use of DTI measures have been shown to have an association between repeated HIE and DTI-derived changes in the brain.

Prior studies of HIE in collision sports have evaluated total changes in abnormal voxels derived from the DTI metrics, but few analyses have evaluated clinical outcome measures that attempt to explain the directional changes in DTI measures.[20] When compared separately, increases and decreases of DTI metrics have different associations with changes in the brain. For instance, increased mean FA and decreased mean MD have been

associated with axonal swelling reducing space between fibers, cytotoxic edema, and inflammation.[21,22] Meanwhile, decreased mean FA and increased mean MD can be indicative of myelin damage, disruption of tissue structure, and axonal damage.[7,23,24] Clinical evidence has shown increases in symptoms, measures of impairment, and the total number of abnormal DTI measures associated with concussion within just a week of the event.[20,25,26] There is also evidence that repeated HIE can lead to long-lasting (several months or years) effects in the brain.[9,10,27,28] There is still a great deal of debate regarding the mechanisms behind these differences, with one explanation being that they represent acute and chronic phases of injury, separately. Investigating the effects of HIE on directional changes in DTI metrics could further elucidate the effects that subconcussive HIE has on the brain, including the kind of damage that occurs, along with possibly the phase of injury (acute vs chronic). It is possible that time-weighted HIE metrics, by taking into account the brain's ability to recover, can describe acute and chronic phases of injury differently. By comparing time-weighted metrics to directional changes in DTI metrics, the relationship between time-weighted metrics and acute/chronic changes in the brain, as well as other directional changes can be assessed. Therefore, the objective of this study is to compare biomechanical metrics of cumulative head impact exposure that consider volume, and severity, as well as some that consider frequency, with directional changes in DTI measures acquired from diffusion data.

Methods

Athletes were recruited from one of three youth football organizations to participate in this study approved by the Wake Forest School of Medicine Institutional Review Board. Written participant assent and parental consent were properly acquired for participation in

the study. Each enrolled athlete was fitted with a Riddell Speed or Revolution football helmet instrumented with a Head Impact Telemetry (HIT) System MxEncoder, which includes a 6-sensor accelerometer array that records and stores head impacts that a participant receives in real-time.[29] A researcher was present at each game and practice to operate the HIT system, ensure that sensors were operational, and record video of each event using a time-synchronized camera. After each season, video was reviewed to validate impacts recorded by the HIT system before analysis. Data for this study was collected over the course of six seasons, from 2012 to 2017. The methods used for data processing have been described in prior studies.[30,31] In order to obtain a control sample, non-contact athletes were also recruited from local youth teams and clubs, such as baseball, swimming, and tennis. Control participants underwent a screening process to ensure that they did not have any history of concussion or participation in contact sports. For all participants, individuals were excluded if they had prior brain surgery or history of traumatic brain injury.

Imaging:

Pre and postseason MRI was acquired on a 3 Tesla Siemens Skyra MRI scanner (mean time between scans was 4.5 ± 0.95 months). Control participants also completed MRI scans at baseline and at a follow-up 3.98 ± 1.07 months later. Each MRI scan was evaluated by a board certified neuroradiologist for structural abnormalities and motion artifacts. Any scans with clinically relevant abnormalities (e.g., tumors and uncharacteristically high white matter lesions) or motion artifacts were excluded from analysis. MRI acquisition and processing has been previously described in Davenport et al. and are abbreviated here.[18] T1-weighted images as well as diffusion data were acquired. Diffusion data was eddy current corrected and tensors fit using the FMRIIB Software Library.[32-36] Voxel-wise DTI

scalar metrics: fractional anisotropy (FA), mean diffusivity (MD), linear anisotropy (C_L), planar anisotropy (C_P), and spherical anisotropy (C_S), were computed using DTI-TK. FA is a measure of the uniformity of the direction of flow of water molecules in white matter, and MD is a measure of the degree of free movement of water molecules.[37] These scalar maps were then warped to Montreal Neurologic Imaging (MNI) space based on the SPM8 normalization from the T1 image. The first DTI protocol parameters included a 10500ms/99ms TR/TE, 90° flip angle, and 2.2mm x 2.2mm x 3.0mm voxel resolution with b-values of 0, 1000, and 2000 s/mm^2. The second DTI protocol parameters included a 12600ms/100ms TR/TE, 90° flip angle, a 2.0mm x 2.0mm x 2.0mm voxel resolution with b-values of 0, 1000, and 2000 s/mm^2.

Each pre-season scalar map was subtracted from the post-season map for each player, creating a delta map for each metric. The same procedures were followed for control subjects, subtracting baseline scalar maps from the follow-up maps. The voxel-wise group mean and standard deviation of the controls' delta maps were used to calculate voxel-wise z-scores for each football player. A voxel was defined as abnormal in the contact sample if its z-score was at least 2 standard deviations (SD) away from the mean of voxel value in the control sample. These represented abnormally high and low scalar values. A cluster threshold requiring a minimum 1 mL contiguous volume was applied to reduce false positives. The number of abnormal voxels 2 SDs above the mean is defined as the number of increases in abnormal voxels, and the number of abnormal voxels 2 SDs below the mean are defined as the number of decreases in abnormal voxels.

Biomechanical Metrics:

Several biomechanical metrics were investigated as independent variables, including number of impacts, risk-weighted exposure (RWE), and three time-weighted cumulative exposure metrics: exponential time-weighted exposure ($TWE_{Exponential}$), inverse time-weighted exposure ($TWE_{Inverse}$), and time until assessment (TUA) (Table 1). Number of impacts is the total number of impacts recorded over a season for an athlete. This metric does not consider the magnitude of the impact or the time it occurred. RWE is a method combining the magnitude and frequency of hits experienced by an athlete by non-linearly weighting each impact by the estimated concussion risk.[38] To compute RWE, the risk of concussion for each impact for each player was calculated using the combined probability risk function (CP) previously described by Rowson and Duma and summed to generate RWE for the season.[39] The logistic regression equation is provided in Table 1, where β_0 is -10.2, β_1 is 0.0433, β_2 is 0.000873, β_3 is -9.2E-7 and a_i and α_i are the peak resultant linear and rotational acceleration, respectively, for each impact.

The equation for each time-weighted metric is provided in Table 1 and further described below. In Table 1, 'X_C' represents the magnitude of a given (i.e., current) impact, 'X_P' represents the magnitude of an impact that occurred before the impact under consideration (i.e., prior to). *'n'* is the total number of impacts the player experienced, *'m'* is the number of impacts that occurred in a preceding time window, where the duration of the time window under consideration is defined by the metric, 'T_C' is the time of the current impact, 'T_P' is the time of a prior impact. The remaining variables specific to each time-weighted metric are further described below.

Table 5. Biomechanical Exposure Metrics (All metrics are unitless, representing injury risk)

Abbreviation	Description	Equation
X	Combined Probability injury risk function	$\left(\frac{1}{1+e^{-(\beta 0+\beta 1 a_i+\beta 2\alpha_i+\beta 3 a_i\alpha_i)}}\right)$
RWE	Risk-Weighted Exposure	$\sum_{i=1}^{n} X_C$
$TWE_{Exponential}$	Exponential Time-Weighted Exposure	$\sum_{i=1}^{n}\left[X_c+\sum_{j=1}^{m}\left[\left(e^{\gamma(T_c-T_p)}\right)*X_p\right]\right]$
$TWE_{Inverse}$	Inverse Time-Weighted Exposure	$\sum_{i=1}^{n}\left[X_c+\sum_{j=1}^{m}\left[\left(\frac{b}{T_c-T_p}\right)*X_p\right]\right]$
TUA	Time Until Assessment	$\sum_{i=1}^{n}\left[\left(\frac{b}{T_c-T_D}\right)*X_c\right]$

For each time-weighted metric, exposure may represent a variety of biomechanical variables, including peak resultant linear acceleration or rotational acceleration. To account for the combined effect of linear and rotational acceleration experienced in each impact and to create a time-weighted exposure metric comparable to RWE, the combined probably of each impact was calculated and used as the measure of *exposure* in each time-weighted exposure metric – $TWE_{Exponential}$, $TWE_{Inverse}$, TUA. Additionally, for each time weighted metric, time was measured in units of hours. Each metric is unitless (except for number of impacts, which is a count), representing injury risk. Each time-weighted metric is described in detail below.

Exponential Time-Weighted Exposure ($TWE_{Exponential}$):

For a given impact (X_C), the CP of each prior impact (X_P) within a specified time window was weighted based on an exponential decay function ranging from 0 to 1, as a function of time between the given impact and the prior impact. An exponential decay constant ($\boldsymbol{\gamma}$ = -

0.3) was multiplied with the time interval (i.e., the time between the current impact and the prior impact) in the exponent (T_c - T_p). A range of exponential decay constants were tested (from -0.1 to -0.5), with little change in the calculated value among constants lower than -0.3. As a result, -0.3 was chosen as the exponential decay constant for this metric. A time window of 72 hours was chosen as literature indicates this is a common timeframe for certain blood biomarker and ion levels associated with traumatic brain injuries to usually return to normal, suggesting some recovery from a concussive head impact.[40-42] It is assumed that this time window would also capture the time needed for the brain to partially recover following sub-concussive hits as there is no data currently available to inform the brain recovery timeframe from subconcussive head impacts. For each head impact, the exponential time-weight was applied to all head impacts occurring less than 72 hours prior to the given head impact. This was iteratively computed for every head impact over the season and summed to generate a single value representing the exponential time-weighted cumulative exposure. For example, if a player receives two impacts one hour apart, the $TWE_{Exponential}$ value for the second impact is equal to the CP of the second impact added to the CP of the first impact scaled exponentially by the time difference between the two impacts (one hour). This is repeated for every impact prior to the current within the 72-hour window. Figure 4 demonstrates the relationship between $TWE_{Exponential}$ and RWE.

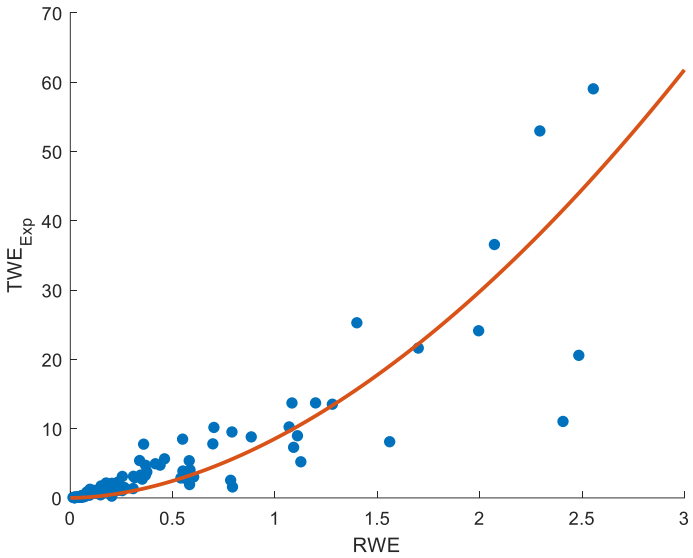

Figure 4. Relationship between $TWE_{Exponential}$ vs. RWE

Inverse Time-Weighted Exposure ($TWE_{Inverse}$):

This method was derived from the work of Merchant-Borna et al, except it uses CP as the exposure metric instead of peak acceleration values.[13] For a given impact (X_C), only impacts occurring on the same day are considered. The time-weighting scale factor employed in this method weights each impact inversely by the time between the given impact and every previous impact occurring on the same day. CP for each impact is added to the CP of every impact that occurred within the same day, each multiplied with a inverse time scale factor of the time difference between the current and that prior impact. The time difference was measured in hours so the smallest scale factor possible is 1/24 (if the two impacts occurred an entire day apart), and the largest scale factor approaches 1/0, if the impacts occur very close together. In this equation, the time difference (T_c - T_p) is between the current and prior impacts respectively, and *'b'* represents a constant that has a value of 1 hour.

Time Until Assessment (TUA):

This method was also derived from Merchant-Borna et al, but uses CP as the measure of exposure instead of peak acceleration values.[13] In this approach, impacts are evaluated relative to the post-season assessment. The CP of each impact is multiplied with the inverse of the time difference between the time of post-season assessment (T_D) and the time of impact (T_c). As a result, impacts closer to the end of the season are weighted more heavily than those that occurred near the beginning of the season. In this equation, the time difference (T_D-T_c) is between the time of post season scan and the given impact respectively, and *'b'* represents a constant that has a value of 1 hour. For example, if an impact occurs 3 months (2208 hours) before post-season assessment, its CP is multiplied by 1/2208 before being added to the cumulative measure for the season.

Statistical Analysis: To evaluate the effect of cumulative HIE on directional changes in the brain, biomechanical metrics were compared with increases in abnormal voxels and decreases in abnormal voxels derived from DTI. Five diffusion-based metrics were used to represent changes in the brain observed through MRI scans: fractional anisotropy (FA), mean diffusivity (MD), linear anisotropy (C_L), planar anisotropy (C_P), and spherical anisotropy (C_S). All DTI metrics were logarithmically transformed prior to analysis, as well as each time-weighted metric. The rationale behind logarithmically transforming time-weighted metrics was to accommodate for skew present in the raw values for these metrics. Collinearity of predictor variables (biomechanical metrics) was evaluated in a prior study and demonstrated the biomechanical variables were not highly associated with each other.[43] Cook's distance (4/n, where n is the number of participants) was used to identify and exclude outliers from each regression. Additionally, covariate adjustment was

conducted to account for differences in age, weight, time between scans, and differences in imaging protocol between seasons. Statistical analysis was completed in SAS v.9.4 (Cary, NC, USA).

Results

95 athletes were enrolled in this study who played in one or more seasons over the course of six seasons of play and had complete and quality MRI data, resulting in 117 player-seasons. The average age and weight of the participants was 11.9 ± 1.0 years and 110.6 ± 21.4 lbs, respectively. Over six years of data collection, 34,039 verified impacts were recorded from this sample of athletes, with an average (± standard deviation) number of impacts per player per season of 290.9 ± 205.8. Summary statistics of biomechanical metrics calculated in this study are provided in Table 6.

Table 6. Summary Statistics of Biomechanical Metrics

Metric	Mean (± Standard Deviation)	Median	95th Percentile	Skewness Coefficient	Coefficient of Variation
Number of impacts	290.9 ± 205.8	222	681.8	0.999	0.707
RWE	0.44 ± 0.58	0.18	1.76	2.056	1.318
$TWE_{Exponential}$	4.87 ± 9.39	1.35	22.13	3.678	1.928
$TWE_{Inverse}$	1088 ± 1855	374	5718	2.593	1.705
TUA	$4.16 \times 10^{-4} \pm 8.97 \times 10^{-4}$	1.85×10^{-4}	1.90×10^{-4}	6.726	2.156

Results of linear regressions are provided in Table 7. Among regressions with increasing abnormal voxels, 96% of comparisons were significant ($p<0.05$), while regressions with decreasing abnormal voxels, only 64% of comparisons were significant. The strongest relationships between biomechanical metrics and increasing abnormal voxels were with log MD. In this set of comparisons, the relationship between MD and $TWE_{Exponential}$ was strongest ($R^2 = 0.1965$), followed by TUA ($R^2 = 0.1837$), number of impacts ($R^2 = 0.1787$),

RWE (R^2 = 0.1628), and $TWE_{Inverse}$ (R^2 = 0.1550). The comparison between log MD and log $TWE_{Exponential}$ was also the strongest relationship observed across all comparisons.

The strongest relationships between decreases in abnormal voxels and biomechanical metrics were with log C_S and number of impacts, followed by C_S and $TWE_{Exponential}$, followed by log FA and number of impacts. The strongest relationship overall was between log C_S and number of impacts (R^2 = 0.1625). Five of the top six ranking relationships involving decreases in abnormal voxels were with log C_S. In this set of biomechanical metrics (where all relationships are significant), time-weighted metrics all outrank RWE, but number of impacts ranks highest. For comparisons between decreases in log FA and biomechanical metrics, only three relationships are significant: number of impacts (R^2 = 0.1547), $TWE_{Exponential}$ (R^2 value = 0.1115), and TUA (R^2 = 0.0860). For comparisons between decreases in log MD and biomechanical metrics, all relationships were significant: log $TWE_{Exponential}$ (R^2 = 0.1031), RWE (R^2 = 0.1028), number of impacts (R^2 = 0.1015), log TUA (R^2 = 0.0993), and log $TWE_{Inverse}$ (R^2 = 0.0920). Relationships between log MD and biomechanical metrics among abnormal decreases (average p = 0.0073 ± 0.0016, average R^2 = 0.0997 ± 0.0046) were generally more significant than those with FA (average p = 0.0394 ± 0.0509, average R^2 = 0.0873 ± 0.0482). Overall, comparisons between cumulative biomechanical metrics and increases in abnormal voxels (average R^2 = 0.1410 ± 0.0328) feature more significant relationships and stronger correlations (i.e., larger R^2 values) than comparisons between cumulative biomechanical metrics and decreases in abnormal voxels (average R^2 = 0.0864 ± 0.0499). For decreases in abnormal voxels, C_S is the DTI metric with the strongest relationships with biomechanical metrics. Plots of

regressions between biomechanical metrics and increases and decreases in log FA voxels can be seen in Figures 5 and 6.

Table 7. Linear Regression Analysis of Biomechanical Metrics and DTI Metrics (bolded, * represents statistically significant relationships $p<0.05$)

Comparisons	Increases				Decreases			
	Covariate Adjustment for age, weight, time between scans and imaging protocol				Covariate Adjustment for age, weight, time between scans and imaging protocol			
	Adjusted R^2	p value	Adjusted R^2 Rank	Total Rank	Adjusted R^2	p value	Adjusted R^2 Rank	Total Rank
FA vs. # Impacts	**0.1681**	**0.0002***	**1**	**4**	**0.1547**	**0.0004***	**1**	**3**
FA vs. RWE	**0.1489**	**0.0005***	**5**	**11**	0.0492	0.0629	4	19
FA vs. $TWE_{Exponential}$	**0.1619**	**0.0002***	**2**	**6**	**0.1115**	**0.0034***	**2**	**7**
FA vs. $TWE_{Inverse}$	**0.1547**	**0.0003***	**4**	**9**	0.0352	0.1184	5	21
FA vs. TUA	**0.1567**	**0.0003***	**3**	**7**	**0.0860**	**0.0121***	**3**	**14**
MD vs. # Impacts	**0.1787**	**0.0001***	**3**	**3**	**0.1015**	**0.0065***	**3**	**10**
MD vs. RWE	**0.1550**	**0.0004***	**5**	**8**	**0.1028**	**0.0064***	**2**	**9**
MD vs. $TWE_{Exponential}$	**0.1965**	**<0.0001***	**1**	**1**	**0.1031**	**0.0063***	**1**	**8**
MD vs. $TWE_{Inverse}$	**0.1628**	**0.0003***	**4**	**5**	**0.0920**	**0.0102***	**5**	**13**
MD vs. TUA	**0.1837**	**<0.0001***	**2**	**2**	**0.0993**	**0.0072***	**4**	**11**
C_L vs. # Impacts	**0.1536**	**0.0004***	**1**	**10**	**0.0824**	**0.0154***	**2**	**15**
C_L vs. RWE	**0.1308**	**0.0014***	**5**	**18**	0.0563	0.0525	4	17
C_L vs. $TWE_{Exponential}$	**0.1403**	**0.0008***	**4**	**16**	**0.0925**	**0.0010***	**1**	**12**
C_L vs. $TWE_{Inverse}$	**0.1413**	**0.0008***	**3**	**14**	0.0168	0.2408	5	23
C_L vs. TUA	**0.1417**	**0.0008***	**2**	**13**	**0.0694**	**0.0290***	3	16
C_S vs. # Impacts	**0.1284**	**0.0016***	**1**	**21**	**0.1625**	**0.0003***	**1**	**1**
C_S vs. RWE	**0.0630**	**0.0384***	**4**	**24**	**0.1491**	**0.0005***	**5**	**6**
C_S vs. $TWE_{Exponential}$	**0.1277**	**0.0016***	**2**	**22**	**0.1580**	**0.0003***	**2**	**2**
C_S vs. $TWE_{Inverse}$	0.0490	0.0684	5	25	**0.1537**	**0.0004***	**3**	**4**
C_S vs. TUA	**0.0996**	**0.0062***	**3**	**23**	**0.1518**	**0.0004***	**4**	**5**
C_P vs. # Impacts	**0.1342**	**0.0012***	**3**	**17**	0.0454	0.0796	2	20
C_P vs. RWE	**0.1409**	**0.0008***	**2**	**15**	0.0503	0.0634	1	18
C_P vs. $TWE_{Exponential}$	**0.1295**	**0.0014***	**4**	**19**	0.0190	0.2205	3	22
C_P vs. $TWE_{Inverse}$	**0.1478**	**0.0005***	**1**	**12**	0.0031	0.3818	5	25
C_P vs. TUA	**0.1290**	**0.0014***	**5**	**20**	0.0146	0.2585	4	24

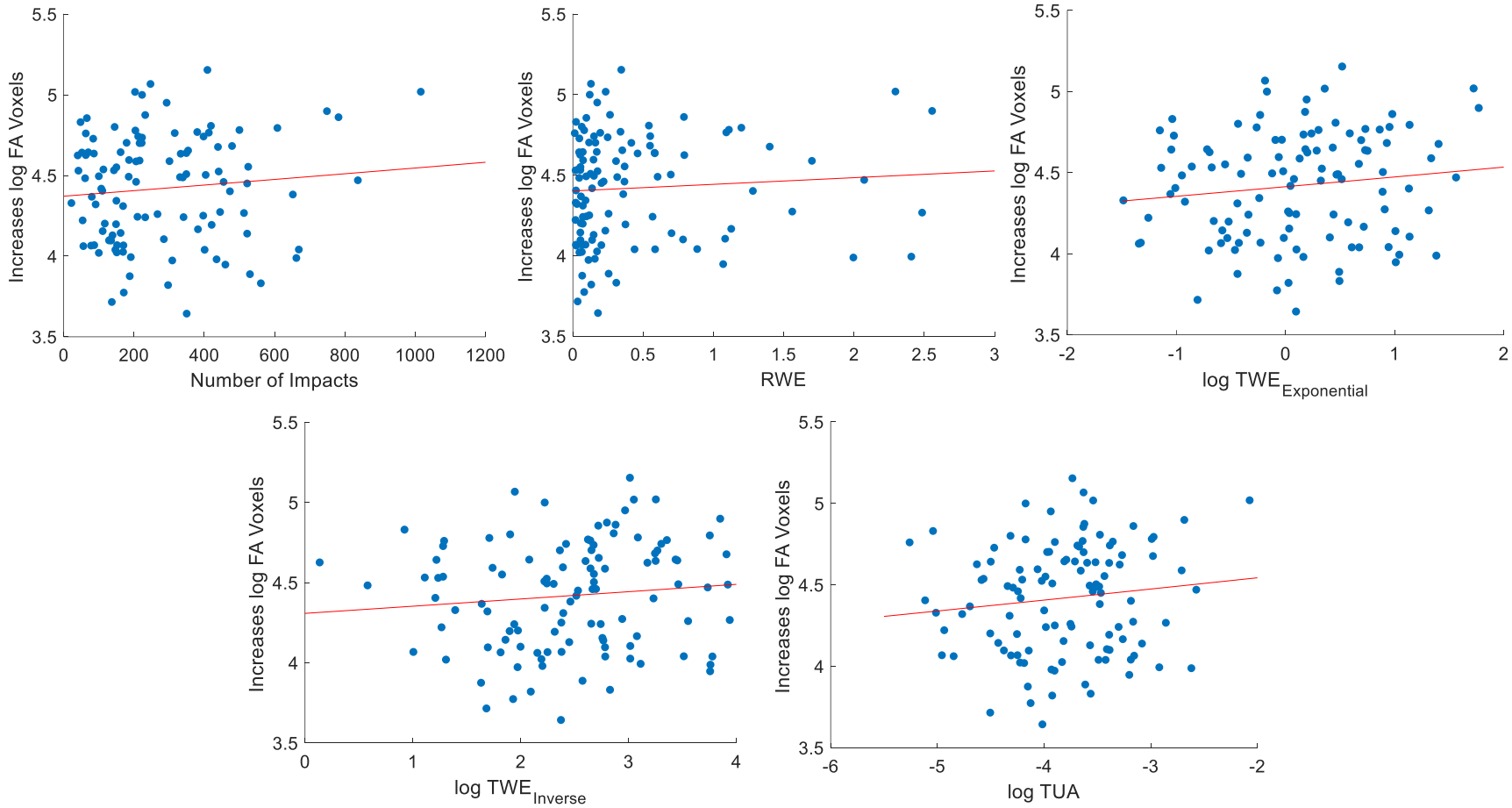

Figure 5. Linear regression between cumulative HIE metrics and increases in abnormal FA voxels

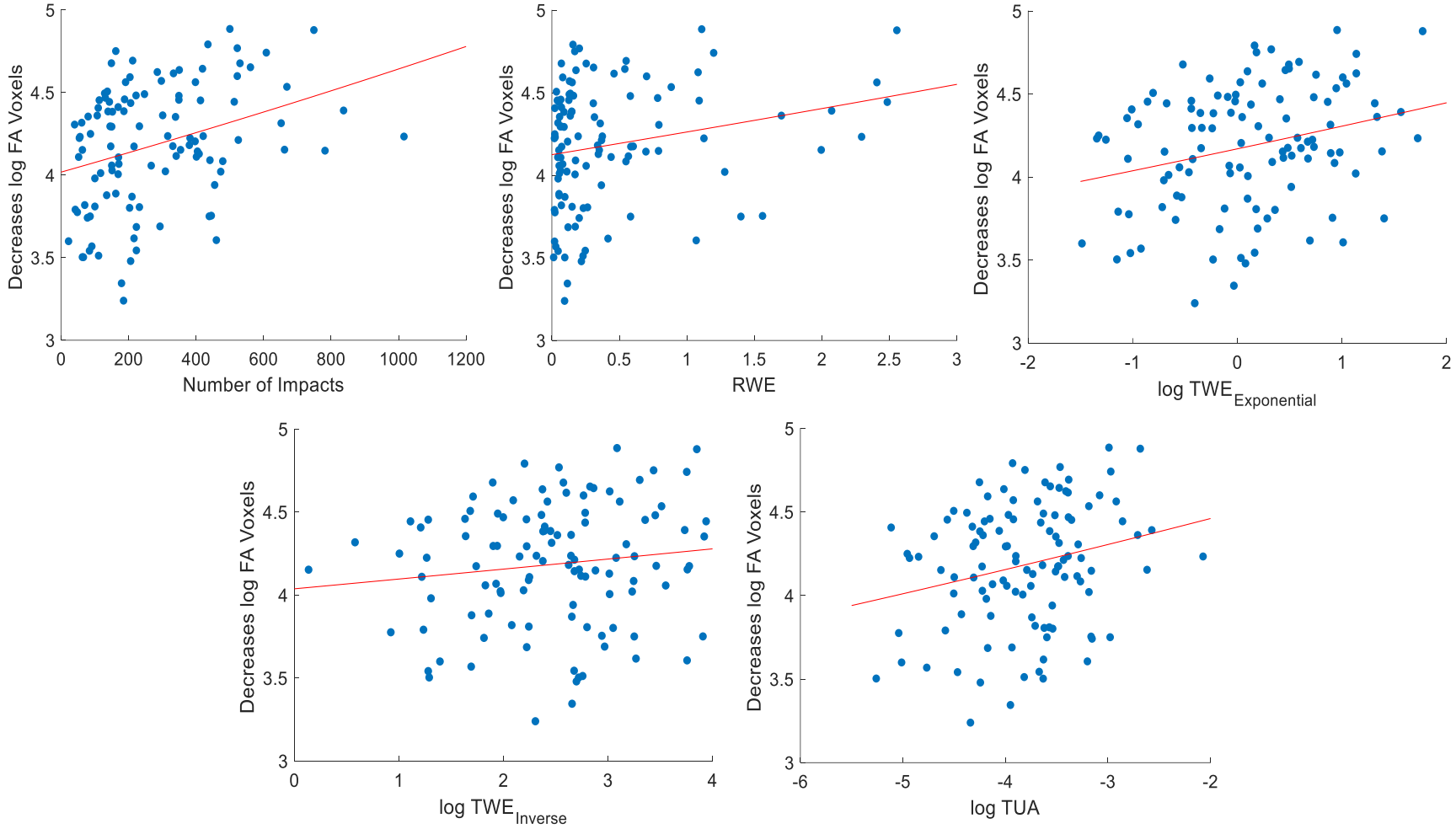

Figure 6. Linear regression between cumulative HIE metrics and decreases in abnormal FA voxels

Discussion

The objective of this study was to determine the relationship between cumulative HIE metrics and increases and decreases in abnormal voxels from DTI metrics. The focus of this study was in youth athletes for whom knowledge of the effects of cumulative HIE is not well understood and potential long-term implications of exposure are of rising concern.[6,44,45] The results indicate there is a significant relationship between cumulative HIE and changes in the brain associated with directional changes in DTI metrics. Comparisons involving increases in abnormal voxels tended to be stronger and more significant than comparisons involving decreases in abnormal voxels. Additionally, of all DTI measures, the number of abnormal MD voxels tended to have the strongest relationships with time-based exposure measures. The results of this study motivate further investigation into the properties of HIE (including volume, magnitude, and timing) that affect directional changes in the brain as a result of repeated impacts.

DTI differs from standard structural MRI (i.e. T1 weighted imaging) as it measures random translational motion of water molecules at a microscopic level.[16] This allows DTI metrics to be more sensitive to changes in white matter integrity than other MRI measurements. DTI metrics have been found to be associated with head impact induced changes in the brain.[46-47] The two primary DTI metrics used in these analyses were FA and MD. FA represents a scalar quantity measuring the fraction of the diffusion tensor that can be ascribed to anisotropic diffusion, while MD represents a scalar quantity that measures the average amount of diffusion in a voxel. C_L, C_P, and C_S each represent sub-measures of FA. Abnormal decreases in FA may reflect chronic phases of injury[16,48] while abnormal increases in FA have been demonstrated to be associated with acute phases of injury.[15,19]

One explanation for this phenomenon is that during the acute phase of an injury, axonal swelling occurs, causing movement of water into the axons and thus increasing FA and decreasing MD (by limiting the direction of flow). In this study we found the strongest relationship among correlations with MD. This may be because unlike FA, which is uniformly low in gray matter and primarily suitable for interrogating changes in white matter fibers, MD is appropriate for describing diffusion in both white and gray matter.[49-53] Our analysis used all voxels in the brain, including both gray and white matter. Accordingly, changes in MD may have been a better measure of global brain changes related to HIE than anisotropy measures of FA, C_L, C_S, and C_P. The stronger relationship with MD, a metric known to be more sensitive in gray matter than other DTI metrics, suggests that gray matter may be the more susceptible tissue type. Of the anisotropic measures, increases in FA, increases in C_L, increases in C_P, and decreases in C_S demonstrated the strongest significant relationships with HIE measures. While these directional trends may represent unknown histological changes in gray matter, such changes in white matter are consistent with axonal swelling or cytotoxic edema.[52,53] In addition to tissue-specific alterations, some diffusion changes may reflect the time course of microstructural change after trauma. Some abnormal diffusion measure increases correlate with acute changes following trauma (increases in FA and C_L), while others correlate with chronic changes (increases in MD and C_P).[23,54,55] The differences in what structural elements these metrics represent (gray matter/white matter, axons, myelin sheath, etc.) in the brain could explain how time-weighted metrics can be used to explain certain types of changes in the brain (including those associated with acute and chronic phases of injury).

The time-weighted metrics presented in this study were first introduced to evaluate the effect of time-weighted cumulative HIE metrics on pre- to post-season changes in DTI, represented as total abnormal voxels (i.e., without regard to direction of change).[43] In general, the relationships observed in the prior study were stronger than those observed in the present study. Focusing on relationships between biomechanical metrics and total changes in log FA voxels, the results were as follows: number of impacts $R^2 = 0.2767$, RWE: $R^2 = 0.1787$, $TWE_{Exponential}$: $R^2 = 0.2624$, $TWE_{Inverse}$: $R^2 = 0.1982$, and TUA: $R^2 = 0.2347$. This supports continued study of total abnormal changes in the brain; however, further understanding of the effects of subconcussive head impacts on short- and long-term brain changes is warranted.

One important finding of the present study is, when isolating directional changes (i.e., increases, decreases in abnormal voxels), cumulative HIE was more strongly correlated with increases compared to decreases. Measures such as increases in FA have been connected to acute phases of injury, while decreases in FA have been connected to chronic phases of injury.[7,23,24,53] However, increases in MD have been connected to chronic phases of injury while decreases in MD have been connected to acute phases of injury. [7,23,24,53] In the present study, participants performed MRI scans at the beginning of each season and at the season's completion. However, the neural effects of subconcussive hits at the beginning of a season may not be manifest in a post-season scan as the brain recovers over time.[56] Yet, the accumulation of impacts may have long-lasting effects on the brain, which become evident in other ways (such as symptoms presenting in the distant future).[27,37] Past work has demonstrated that indicators of injury degrade over time (concussion scores,

blood biomarkers, etc.) which support the idea of increasing frequency of collection of data that proves injury. [26,40-42] There may be a benefit to performing more frequent in-season imaging of participants to understand the effects of HIE on acute or short-term changes in the brain. This may also inform time-windows to recovery following subconcussive head impacts which are important in the development of robust time-weighted cumulative exposure metrics. Chronic changes may be explained by relationships involving increases in MD. This may be due to the fact that MD represents changes in gray matter as opposed to white matter. Future work could investigate the tissue types in conjunction with HIE-induced brain changes. Additionally, the unique information contained in metrics like $TWE_{Exponential}$ (which scales risk by time between impacts) and TUA (which scales risk by time until assessment) could be combined to a single metric which captures the accumulation of impacts over time, relative to the post-season assessment. This would explain why $TWE_{Exponential}$ and TUA both had stronger correlations than other biomechanical metrics in certain analyses.

In this study, time-weighted metrics weighed impacts based on time differences. However, based on the strength of relationships involving number of impacts (a solely volumetric measure), there may also be value in investigating weighing impacts based on biomechanics as well. For instance, the contribution of any impact on the cumulative metric could be weighed differently based on the magnitude of that impact (e.g. a 20g impact could be weighed less than a 50g impact, or vice-versa). Additionally, this study used time windows of 72 hours. This is based on literature suggesting that levels of blood biomarkers, neurotransmitters, and ion levels are elevated for approximately this period following impacts.[40,41] Different time windows were tested in preliminary phases of this research, but

future studies could test the efficacy of expanding the time window, as well as adjusting the decay functions of time-weighted metrics to further incorporate older impacts.

In this study, multiple significant relationships between cumulative HIE metrics and directional changes in DTI metrics are presented, indicating that there is a link between cumulative HIE and chance of injury; however, not all changes in the brain can be attributed to sports-induced head impacts. A number of factors including age, diet, stress, genetics, disease, etc. could conceivably contribute to measurable changes in the brain. Additionally, to collect the biomechanical data needed for developing cumulative HIE metrics, the HIT system was used. This system has some measurement error relating to impact detection and acceleration measurements. Nevertheless, previous studies have used the HIT system and verified its accuracy.[57]

The clinical impact of this research lies in mitigating the incidence of brain injury by identifying the underlying factors behind it. HIE is associated with an increased chance of injury. In a study by Stemper et al., concussed athletes had greater HIE than the matched control group.[58] If the specific features of HIE that contribute to injury could be identified and understood, modifications could be made to how football is played or the protective equipment that is worn in order to reduce the chance that players get injured.

Conclusion

The objective of this study was to ascertain the relationship between time-weighted cumulative HIE metrics and directional changes in DTI measures. The results indicate that time-weighted cumulative HIE metrics better relate to abnormal increases, and that they tended to have stronger relationships with directional DTI metrics than volumetric and/or

risk-based metrics that do not consider the effect of time. For abnormal increases in DTI metrics, time-weighted HIE metrics rank higher than RWE for FA, MD, and CL. For abnormal decreases, time-weighted HIE metrics rank higher than RWE for CS. For both increases and decreases, time-weighted HIE metrics never rank higher than number of impacts for FA and CS. Time-weighted metrics seem to better explain brain changes associated with directional DTI metrics than RWE, while number of impacts ranked the highest correlate in a majority of cases. The findings of this study provide support to the idea that a time-weighted cumulative HIE metric can provide new and valuable information regarding the effects of repeated subconcussive head impacts. Future studies should consider investigating in-season assessments to better understand the effects of time-weighted head impact exposure on changes in the brain associated with directional DTI metrics.

Acknowledgments

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CHAPTER IV: SUMMARY OF RESEARCH

The research presented in this thesis investigated the factors associated with sports-induced head injury, and its findings provide a substantial addition to the growing body of knowledge in this field. By collecting biomechanical head impact exposure data from youth football players and corresponding diffusion-based MRI scans of players, the following objectives were able to be accomplished:

1. Develop novel time-weighted cumulative head impact exposure metrics and compare their values with white matter changes in the brain as measured with DTI scans to determine the importance of time in considering chance of injury.
2. Compare time-weighted cumulative head impact exposure metrics with abnormal increases and decreases in DTI metrics separately in order to investigate the relationship between time-weighted metrics and acute and directional changes in the brain.

By studying the utility of time-weighted cumulative head impact exposure, the importance of considering when impacts occur relative to other events can be seen. The benefit of time-weighting can also be evaluated in the context of explaining certain types of effects on the brain, providing additional information on the phenomenon and circumstances that contribute to head injury following repeated head impacts and how they might be mitigated. The research presented in Chapter II is in preparation for submission to the Journal of Neurotrauma, and the research in Chapter III is planned to be published in the American Journal of Neuroradiology.

CURRICULUM VITAE

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EDUCATION

Virginia Tech-Wake Forest University, Winston-Salem, NC August 2019 – September 2021

Master of Science in Biomedical Engineering

GPA: 3.56/4.0

Georgia Institute of Technology, Atlanta, GA August 2015 – May 2019

Bachelor of Science in Biomedical Engineering

GPA: 3.55/4.0

Dean's List

SKILLS

Computational Modeling, Finite Element Modeling (LS Dyna, LS PrePost), MATLAB, Statistical Software (SAS, JMP, SPSS), Solidworks, ASPEN Plus, Scanning Electron Microscope (SEM), Clean Room skills, Wet Lab skills, Image Analysis, High Speed Videography, Particle Vapor Deposition (PVD), 3D Printing, Silicone Molding

PROFESSIONAL EXPERIENCE

Center for Injury Biomechanics, Winston-Salem, NC
August 2019 – May 2021
Graduate Research Associate

- Assisted in conduction on-field head impact acceleration data collection of high school football players over the course of a season using helmet-mounted accelerometer arrays and video recording of events
- Assisted in cognitive testing and clinical imaging of recruited players post-season
- Performed video analysis using Kinovea to assess validity of recorded head impacts
- Developed novel ideas for research projects and submitted applications for fellowship grants
- Communicated findings in oral and poster presentations at research conferences

SENIC Program, Joint School for Nanoscience and Nanoengineering, Greensboro, NC
May 2016 – July 2016
Intern

- Fabricated thin flexible sensors using polydimethylsiloxane (PDMS) and thin films of gold for use in cardiac sensors
- Researched viability of A549 lung cells with exposure to nanoparticles and upon undergoing stretching
- Worked in Clean Rooms, and used equipment such as SEM, and PVD

Hu Biolocomotion Lab, Atlanta, GA
August 2017 – May 2019
Undergraduate Research Assistant

- Researched biomechanics of honey bee pollen pellet formation and removal behaviors
- Designed experiments and constructed apparatuses using 3D printing and laser cutting machines
- Analyzed results of experiments using high speed videography, video analysis, and scanning electron microscopy
- Communicated findings in written and oral form at multiple university-sponsored undergraduate research symposia

PROJECTS

Mathematical Modeling of Traumatic Brain Injury in Football
Aug 2019-May 2021
Center for Injury Biomechanics, Wake Forest University, Winston-Salem, NC

- Developed 3 novel acceleration-based, time-weighted injury risk metrics using data from 95 football players over 6 seasons to determine players' chance of injury as a result of repeated head impact exposure in contact sports such as youth football
- Discovered that incorporating time between impacts in a series in the injury risk metric can increase its ability to predict injury, which could substantially reduce the incidence of mild traumatic brain injuries
- Conducted statistical analysis using SAS and JMP
- Presented findings at multiple conferences and authored two journal articles currently in process of submission for publication

Prototyping of Improved Gastrostomy Feeding Tube - Senior Design Project,
Jan 2019-May 2019
Georgia Tech, Atlanta, GA

- Developed an improved gastrostomy tube to prevent migration into stomach and minimize painful side-effects
- Created an articulated model of novel feeding tube to solve visualization problem that served as the basis for future iterations
- Developed novel design and prototyped working model using Solidworks, 3D printing, and silicone molding.
- Worked closely with resident at Emory University Hospital Midtown (Atlanta, GA)

Development of Milk Freshness Detector – Biomedical Engineering Design Project
Aug 2017-Dec 2017
Georgia Tech, GA

- Researched science of milk spoilage and identified design parameters
- Developed a bottle and cap device with multiple sensors to detect the freshness of milk
- Used Arduino, chemical analysis, client interviews, and market analysis to develop project

ORAL PRESENTATIONS

Puvvada, S., Davenport, E., Holcomb, J., Miller, L., Whitlow, C., Powers, A., Maldjian, A., Stitzel, J., Urban, J. (June 2020). The Relationship Between Time Weighted Cumulative Head

Impact Exposure and Abnormal White Matter Changes in the Brain. Presented at Summer Biomechanics, Bioengineering, and Biotransport Conference (SB3C) Virtual Conference.

POSTER PRESENTATIONS

Puvvada, S., Davenport, E., Holcomb, J., Miller, L., Whitlow, C., Powers, A., Maldjian, A., Stitzel, J., Urban, J. (October 2020). Time Weighted Cumulative Head Impact Exposure and Abnormal White Matter Changes in the Brain. Presented at the Biomedical Engineering Society (BMES) Annual Virtual Meeting.

Puvvada, S., Davenport, E., Holcomb, J., Miller, L., Whitlow, C., Powers, A., Maldjian, A., Stitzel, J., Urban, J. (August 2020). The Relationship Between Time Weighted Cumulative Head Impact Exposure and Abnormal White Matter Changes in the Brain. Presented at the School of Engineering and Biological Sciences (SBES) Virtual Symposium.

PUBLICATIONS

Banerjee S., Zhang X., Puvvada S., Agarwal R.. Process simulation of oxy-combustion for maximization of energy output using ASPEN plus. Int J Energy Environ. 2014;5(5):575-582.