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Comparison of Season-Long Diffusivity Measures in a Cohort of Non-Concussed Contact and Non-Contact Athletes

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Abstract

Introduction—Concern surrounding short- and long-term consequences of participation in contact sports has become a significant public health topic. Previous literature utilizing diffusion tensor imaging in sports-related concussion has exhibited notable variety of analysis methods and analyzed regions of interest, and largely focuses on acute effects of concussion. The current study aimed to compare diffusivity metrics across a single season within athlete cohorts with no history of concussion.

Methods—A prospective cohort of 75 contact and 79 non-contact division I athletes were compared across diffusion tensor imaging metrics (i.e., TRACULA); examinations were also performed assessing the relationship between neuroimaging metrics, head impact exposure metrics (in-helmet accelerometer), and neurocognitive variables. Assessment occurred at pre-and post-season time points.

Results—Seasonal changes in fractional anisotropy and mean diffusivity values did not differ between athlete cohorts, nor did they differ within cohort groups, across pre- and post-season scans. Specific to contact athletes, positive associations were found between uncinate fasciculus mean diffusivity values and season linear acceleration ($p = .018$), season rotational acceleration ($p = .017$), and season hit severity ($p = .021$).

Conclusions—Results suggest an influence of impact frequency, type, and severity on white matter integrity in select brain regions in contact athletes. Current findings expand our knowledge

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of anatomical changes over the course of a single season, and underscore the importance of considering methodology when interpreting findings in this population, as differing image analysis techniques may lead to different conclusions regarding significant effects.

Keywords

sport-related concussion; diffusion tensor imaging; TRACULA; white matter integrity

Concern regarding potential long-term consequences of participation in contact sports, including the relationship with later in life neuroanatomical changes, has become a significant public health topic. In assessing sports-related neuroanatomical changes, prior studies have commonly examined white matter integrity using diffusion-weighted imaging (DWI; Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012; Kraus et al., 2007; Mayer et al., 2010). Although much of the scientific literature in this area has focused on concussions (see Cubon, Putukian, Boyer, & Dettwiler, 2011; Henry et al., 2011; Maugans, Farley, Altaye, Leach, & Cecil, 2012; Zhang et al., 2010), a smaller number of studies have looked for neuroanatomical changes in non-concussed individuals involved in contact sports (see Koerte, Ertl-Wagner, Reiser, Zafonte, & Shenton, 2012; McAllister et al., 2014), often using non-contact sport participants for comparison. The present study furthers this line of inquiry by providing further comparisons between contact athletes without concussions and non-contact athletes using a method untested in this population.

Diffusion Weighted Imaging Analysis Methods

Previous literature on DWI in sports-related concussion has primarily employed diffusion tensor imaging (DTI), though with a notable variety of DTI analysis methods and analyzed regions of interest (ROIs). Studies assessing white matter integrity can largely be divided between voxel- or ROI-based approaches (see McAllister et al., 2014; Zhang et al., 2003), including statistical parametric mapping (SPM; see Bazarian et al., 2012; Chappell et al., 2006; Henry et al., 2011), tract-based methods, including Tract Based Spatial Statistics (TBSS; see Cubon et al., 2011; Koerte et al., 2012; Zhang et al., 2010), and various tractography techniques (see Maugans et al., 2012; Zhang et al., 2010; Zhang, Heier, Zimmerman, Jordan, & Uluğ, 2006; Zhang et al., 2003). Commonly assessed ROIs include the corpus callosum, internal capsule, superior and inferior longitudinal fasciculi, anterior and posterior thalamic radiations, corticospinal tracts, temporal and frontal gyri, and the putamen/globus pallidus (see Asken, DeKosky, Clugston, Jaffee, & Bauer, 2017; Gardner et al., 2012).

While the TBSS approach has been successful in analyzing diffusion weighted images, it relies on registering participants to a common template and cannot ensure that any one voxel corresponds to the same tract across different individuals. In contrast, Tracts Constrained by Underlying Anatomy (TRACULA) is an anatomically informed tractography approach that constrains the range of possible diffusion directions based on the anatomical configuration of white matter tracts. This aims to enhance the comparability of major white matter tracts across subjects. TRACULA uses prior distributions of the neighboring anatomical structures of each white matter tract derived from an atlas and combines this with FreeSurfer cortical and subcortical segmentation to constrain the tractography solutions. In theory, this eliminates the need for user-drawn ROIs or the need to manually set thresholds for tract angle and length. Thus, a primary benefit of the TRACULA approach is the automaticity of this form of analysis.

Two prior studies specific to the broad mTBI population have compared DWI approaches across a single sample. Yeh and colleagues (2017) used various DWI techniques to assess diffusion changes in a cohort of 202 armed services members with a positive history of blast-related mTBI and 40 healthy controls. No group differences were found using a voxel-wise analysis. However, analyses using tract profile and tract-specific analyses, including Automated Fiber Quantification (AFQ) and TRACULA, revealed differences among groups, most prominently within frontal fiber tracts. Goodrich-Hunsaker and colleagues (2018) evaluated TBSS, deterministic tractography via AFQ, and probabilistic tractography via TRACULA to assess white matter integrity in a cohort of adolescents with an acute history of mTBI and/or mild orthopedic injuries. The TBSS approach linked white matter changes related to age to all white matter tracts, while AFQ and TRACULA identified age-related changes within the corpus callosum, cingulum bundle, corticospinal tract, inferior and superior longitudinal fasciculi, and uncinate fasciculus. Overall, the authors argued that while the results were largely consistent across the three DWI approaches, it appeared that AFQ and TRACULA provided improved sensitivity and tract-specific results.

DTI in Non-Concussed Athletes

To date, while studies have examined white matter integrity in individuals recovering from a concussive injury, little research has investigated the potential occurrence of white matter changes during a single season of contact sports in athletes without diagnosed concussion. This gap in the literature merits further study, given prior work suggesting that the accumulation of repetitive head impacts may be a risk factor for the development of neurodegenerative illness (see Baugh et al., 2012; Gavett, Stern, & McKee, 2011).

Two prior studies have assessed white matter integrity in non-concussed athletes. Koerte and colleagues (2012) compared diffusion metrics between 40 adult soccer players and 11 elite-level swimmers using voxel-wise analysis. Results suggested higher levels of radial diffusivity (RD) and axial diffusivity (AD) within the corpus callosum in soccer players relative to swimmers. Group differences in measurements of fractional anisotropy (FA) and mean diffusivity (MD) were non-significant. Notably, results of cluster analyses suggested that the higher RD and AD values in soccer players were not related to age or years of athletic participation, suggesting the influence of outside variables such as repetitive head contact. McAllister and colleagues (2014) examined changes in white matter integrity in targeted atlas-based ROIs across contact and non-contact athletes without concussion over the duration of a single athletic season. Participants included 80 contact athletes (football and ice hockey) and 79 non-contact athletes (e.g., track, crew, Nordic skiing, etc.) who underwent pre- and post-season DTI scans and neurocognitive evaluation. Head impact exposure (HIE) data were collected on the contact athletes via the use of in-helmet accelerometers. The study found a relationship between HIE, diffusion metrics, and decreased performance on a verbal learning and memory task over the course of a single season. Additionally, the authors reported a significant group difference in MD values within the corpus callosum as well as differences in FA values within the amygdala. HIE measures of exposure were also correlated with white matter changes within the corpus callosum, amygdala, cerebellar white matter, hippocampus, and thalamus (McAllister et al., 2014).

Present Study

The literature on DWI in sport-related concussion and repetitive head impact varies in methodological approaches. While some authors suggest that tractography approaches may be more sensitive to white matter changes (Goodrich-Hunsaker et al., 2018), no prior study has used such an approach to examine differences related to repetitive head impacts in the absence of concussion. The present study sought to expand the literature regarding white matter changes in single season of athletic competition by studying non-concussed contact and non-contact athletes with TRACULA. We hypothesized that contact athletes would differ from non-contact athletes with respect to diffusivity measures (i.e., FA and MD metrics). Additionally, we hypothesized that diffusivity measures would show a relationship with neurocognitive measures of processing speed, attention, and executive functions, as well as with head impact exposure (HIE) over the course of the season.

Methods

For a detailed summary of procedures relating to data collection and recruitment, including informed consent and imaging methodology, please see McAllister et al. (2014). The following is a brief synopsis of these participants and study procedures, highlighting aspects unique to the current study.

Participants

Participants included two athlete cohorts enrolled at Dartmouth College between 2007 and 2011; this cohort represented the same sample of participants utilized previously by McAllister and colleagues (2014). Study participation was offered to all members of designated contact (football, men's and women's ice hockey) and non-contact (track, crew, Nordic skiing, etc.) athletic teams. Exclusion criteria for the contact athletes in this analysis included diagnosis of a concussion (resulting in the exclusion of all post-injury scans), significant medical comorbidities, and current psychiatric conditions. Exclusion criteria for the non-contact participants also included any prior history of concussion. A history of concussion was identified by each student's respective athletic trainer, or by a trained physician in instances in which the athlete was sent to the emergency department. When available, medical records were reviewed, including computed tomography (CT) scan results. Details regarding injury history were subsequently confirmed via diagnostic interview performed by one of the authors (TWM). The contact athlete group reported an average of 1.41 ± 0.69 sustained concussions prior to their season of study. Consistent with previous literature, participants were not excluded based on handedness (see Mayinger et al., 2018; McAllister et al., 2014). However, two participants were excluded from the current study due to poor performance on a stand-alone performance validity test (i.e., Word Memory Test; Green, Iverson, & Allen, 1999) based on recommended cutoff scores. One additional participant was excluded due to the potential for a prior history of a more moderate traumatic brain injury. Overall, a total of 274 scans met the criteria for analysis.

Procedures

Diffusion Weighted Imaging—In the current study, TRACULA v. 1.60.2.1 with FreeSurfer version 6.0 was used. While the software was generally effective, tracts across several participants representing a few percent of the total were incorrectly defined and required manual adjustments to control points to ensure accurate tract-related values. For additional information regarding TRACULA, readers are referred to Yendiki et al. (2011).

FA and MD values were selected as the primary diffusivity metrics of the current study as both have been shown to be reflective of axonal integrity and may serve as injury biomarkers. While RD and AD have been suggested as additional markers of axonal integrity (Koerte et al., 2012), these values can be difficult to interpret due to complex structural design and crossing tracts (Wheeler-Kingshott & Cercignani, 2009). Primary ROIs included the corpus callosum, anterior thalamic radiations, cingulum, and uncinate fasciculus, due to their common implications in previous DTI literature specific to sport-related concussion, as well as availability as defined tracts in TRACULA.

Assessment of Cognitive Abilities—All participants completed a neuropsychological evaluation during both pre- and post-season visits; tests included those assessing cognitive domains commonly impacted by head trauma, including processing speed, attention, and executive functioning. Specific tests included selected subtests of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001; Color-Word Interference, Verbal Fluency, and Trail Making Tests), the Gordon Continuous Performance Test (CPT; Gordon, McClure, & Aylward, 1996), the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977), and selected subtests (i.e., Digit Span and Digit Symbol-Coding) of the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III; Wechsler, 1997). The Word Reading subtest of the Wide Range Achievement Test, 4th Edition (WRAT-4; Wilkinson & Robertson, 2006) was also administered as a proxy for baseline verbal intellectual ability.

Assessment of Head Impact Exposure—Study participants wore helmets instrumented with HIT System technology (Riddell, Inc., Rosemont, IL; Simbex, Lebanon, NH) to record all head impacts during organized team activities (i.e., both practice and competition settings). All impacts which registered or exceeded a force of 14.4g were wirelessly transmitted to a sideline laptop for data analysis and storage. Key biomechanical variables were chosen *a priori* for the study, and a subset were used in this analysis based on prior work. These included number of head impacts, 95th percentile of peak linear acceleration, 95th percentile of peak rotational acceleration, and 95th percentile of a calculated impact severity score (HITsp), each calculated over specific time intervals for each individual player. A season time interval extended backward from each scan to the subject's initial pre-season scan. Additionally, values reflecting recent play were calculated from a shorter interval (14 days) preceding each scan. The season-long and 14-day time periods were intended to account for the cumulative effects of an entire season of play and more transient effects of recent head impact exposure.

Statistical Analyses

All statistical analyses were performed with R (R Core Team, 2013), version 3.5.1. Prior to conducting inferential parametric statistics, we examined the distributions of all diffusivity, HIE, and neurocognitive variables to ensure that test assumptions were met. To perform contact versus non-contact athlete comparisons, generalized estimating equation (GEE) models were used for both FA and MD diffusivity metrics. GEE models were selected as they can incorporate repeated measures, allowing accurate results with a varying number of samples per subject. These models included visit type (i.e., pre-season vs. post-season), WRAT-4 word reading score, age, scanner epoch (accounting for significant changes to the scanner environment and software upgrades), and subject motion (see Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014). Both age ($p = .024$) and WRAT-4 word reading score ($p = .001$) differed significantly between contact and non-contact groups. To assess the relationship between each HIE variable and diffusivity metric, GEE models with base covariates and two versions of that HIE variable (i.e., season-long and 14-day values) were created in order to determine the impact of a season-long accumulation of impacts above and beyond any acute impact effects. Finally, to evaluate the functional and/or cognitive impact of diffusivity measures overall, GEE models with the same base covariates for FA and MD metrics were performed to determine the relationship between postseason neuropsychological test performance and diffusion metrics across the entire sample.

Results

Sample Characteristics

A total of 274 scans from 75 contact sport athletes and 79 non-contact sport athletes were included in analyses. These participants were a subset of those studied in McAllister and colleagues (2014) for whom scan data passed TRACULA quality assurance procedures. Not all study participants returned for post-season scans; however, the proportion of participants who returned did not differ between contact and non-contact groups. Table 1 shows sample demographic characteristics for the two groups, as well as descriptive statistics for HIT variables (i.e., 95th percentile peak linear acceleration, peak rotational acceleration, and HITsp). As described, HIT variables were aggregated over the season as well as a 14-day window prior to the post-season scan.

Within and Between Group Comparisons of Diffusivity Measures for Contact and Non-contact Athletes

To control for multiple comparisons, a Bonferroni correction was applied, rendering an alpha level of .006 (i.e., .05/8). Pre-season FA and MD values did not differ between contact and non-contact groups across the assessed ROIs (see Table 2). Furthermore, FA and MD changes across a single season in non-contact athletes were also non-significant. For contact athletes, no statistically significant longitudinal differences in FA values were found across the four assessed ROIs. Positive, trend level differences ($p < .05$) were found between pre- and post-season MD values within the uncinate fasciculus and cingulum bundle; however, these differences did not survive Bonferroni correction. Differences in the corpus callosum and anterior thalamic radiations did not approach significance.

Relationship between Head Impact and Diffusivity Measures

The relationship between HIT variables and diffusivity measures was assessed for each ROI. Bonferroni correction rendered an alpha level of .002 (i.e., .05/32). Positive associations (p < .05) were found between uncinate fasciculus MD values and season linear acceleration, season rotational acceleration, and season hit severity; however, these results did not survive Bonferroni correction (see Table 3). No associations between HIT variables and FA diffusivity metrics were found across any of the assessed ROIs other than a trend level negative association between corpus callosum FA values and season linear acceleration.

Relationship between Cognitive Performance and Diffusivity Measures

Associations between performance on neuropsychological tasks and diffusivity measures across the entire sample were examined for each ROI using a Bonferroni corrected alpha value of .003 (i.e., .05/18). Overall, there were no relationships between cognitive performance and diffusivity metrics that remained after Bonferroni correction, although some interesting relationships were observed prior to correction. For the corpus callosum, FA values were positively associated with response time on the simple vigilance and distractibility trials of the Gordon CPT, as well as negatively associated with performance on the PASAT (2.0 second pacing). MD values were positively associated with performance on the WAIS-III Digit Symbol-Coding measure, and negatively associated with performance on the Letter-Number Sequencing trial of the D-KEFS Trail Making Test. For the anterior thalamic radiations, FA values were negatively associated with performance on the D-KEFS Category Fluency subtest. For the cingulum, FA values were negatively associated with performances across the D-KEFS Category fluency subtest, D-KEFS Sorting Total Recognition score, and the PASAT (both 2.0 and 3.0 second pacings). MD values were positively associated with performance across the PASAT (3.0 second pacing). Finally, for the uncinate fasciculus, MD values were positively associated with performance on the D-KEFS Category Fluency subtest, as well as the PASAT (2.0 and 3.0 second pacing) (see Table 4).

Discussion

The results of the current study do not suggest differences in white matter diffusion metrics between collegiate contact and non-contact varsity athletes when studied across a single season using DTI and a probabilistic tractography approach when applying a strict Bonferroni correction for statistical significance. However, the results do suggest an influence of impact frequency, type, and severity on white matter integrity in select brain regions (i.e., the uncinate fasciculus) in contact athletes who have not been diagnosed with a concussion throughout the season, and thus point to possible subtle effects of cumulative repetitive head impacts over time. For example, within the uncinate fasciculus, pre- and post-season differences in contact athlete MD values, as well as positive associations between MD values and season linear acceleration, season rotation acceleration, and season hit severity could suggest evidence of increased water content, potential inflammation, and greater overall cellular disorganization in contact athletes occurring over the course of a single season. Outside of the uncinate fasciculus, negative associations between corpus callosum FA values and season linear acceleration could also suggest evidence for a reduction of axonal integrity in contact athletes.

Importantly, the results of the current study cannot be accounted for by the effects of impacts sustained in the two weeks prior to post-season scans, lending credence to the notion that the current results may reflect the effects of season-long athletic participation. Furthermore, the discrepancy between diffusivity measures, with MD values apparently more sensitive to mild head impact measures than FA values, is consistent with previous research. For example, Messé and colleagues (2010) found an increase in MD but no change in FA metrics in individuals diagnosed with mTBI (Glasgow Coma Scale = 13–15) using TBSS imaging methodology. Likewise, research has found that MD values were more sensitive compared to FA values in detecting white matter changes in early-stage Alzheimer's disease (Acosta-Cabronero, Williams, Pengas, & Nestor, 2010). Overall, it may be that MD values are more sensitive to mild axonal injury or structural white matter abnormalities (Acosta-Cabronero et al., 2010; Beaulieu, 2002; Cubon et al., 2011), whereas FA values become a stronger predictor as brain injury or abnormality severity increases (Perlbarg et al., 2009).

In our prior work using this cohort, an ROI-based approach was utilized to examine differences in FA and MD in the corpus callosum, cerebral and cerebellar white matter, brainstem, thalamus, hippocampus, and amygdala, as defined by the WFU PickAtlas (NITRC, 2007) software package. While the current analysis also examined corpus callosum areas, these differed greatly: the ROI definition follows the body of the corpus callosum from the genu to the splenium (Witelson, 1989), while the TRACULA forceps major and forceps minor regions include only the splenium and genu, respectively, as well as their radiations to occipital and frontal lobe areas. Other white matter tracts investigated in the current study (i.e., anterior thalamic radiations, cingulum, and uncinate fasciculus) differed from our prior study and were selected based in part on ROIs defined by TRACULA. Differences in processing approach and ROI definition are believed to account for the lack of a significant finding in the corpus callosum in the current analysis, when an effect was seen in our and others' prior work (McAllister et al., 2014, Koerte et al., 2012). Overall, the differences between the results using the current approach to DTI processing (TRACULA) and the ROI-based approach used in our previous study on this cohort (McAllister et al., 2014) highlight the importance of considering methodology when interpreting MRI study findings. This difference suggests that complementary information may be gained from the use of alternative image processing and analytic approaches.

One ROI, the uncinate fasciculus, and its possible vulnerability to cumulative impacts warrant further attention, as results suggested positive associations between MD values and HIE variables, despite not meeting more conservative alpha thresholds. The current study is not the first in the sport-related concussion literature to identify anatomical correlates within this white matter tract using DWI approaches (see Asken et al., 2017; Gardner et al., 2012). Briefly, the uncinate fasciculus connects the orbitofrontal cortex to the anterior temporal lobes via a bidirectional monosynaptic pathway (Von Der Heide, Skipper, Klobusicky, & Olson, 2013). Research has suggested that, due to its location, the uncinate fasciculus is vulnerable to immediate impact and shearing-related injuries and is often affected by TBI-related white matter damage (Ewing-Cobbs & Prasad, 2011; Johnson et al., 2011; Seo et al., 2012). Of note, the uncinate fasciculus does not reach its peak developmental maturation level until the third decade of life (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Lebel et al., 2012), which suggests that adolescents and young adults may be more susceptible to developmental disruption as a result of concussion or repetitive head impacts.

Disruption of the uncinate fasciculus has been linked to several neurologic conditions, most notably frontotemporal dementia (FTD), a progressive neurological condition characterized by degeneration of the frontal and temporal lobes (Weder, Aziz, Wilkins, & Tampi, 2007). To be clear, research does not suggest that uncinate fasciculus disruption causes FTD (Von Der Heide et al., 2013). However, research has suggested that diminished integrity within the right and left uncinate fasciculi identified via FA values has been shown in individuals with the behavioral variant of FTD (Zhang et al., 2009; Piguet, Hornberger, Mioshi, & Hodges, 2011; Mahoney et al., 2012). Other work has suggested that when compared to individuals with Alzheimer's disease, patients with the behavioral variant of FTD exhibited decreased FA values bilaterally within the uncinate fasciculus (Tartaglia et al., 2012), and that damage to the left uncinate fasciculus was a predictor of the behavioral variant of FTD, as well as of overall degeneration in these individuals (Agosta et al., 2012).

The relationship between HIE measures and white matter integrity within the uncinate fasciculus is particularly noteworthy given the rapid increase in publications and discussions surrounding the ties between repetitive head trauma and CTE. There appears to be significant symptom overlap between the behavioral variant of FTD and CTE, namely social disinhibition, impulsivity, executive dysfunction, and personality changes (Schoenberg & Duff, 2011; Stern et al., 2013). It is important to appreciate that neurodegenerative conditions are rarely composed of a single type of abnormal pathology (Solomon & Zuckerman, 2014). For example, within the population used by McKee and colleagues (2013) in describing pathological CTE, a significant minority of individuals with CTE also displayed pathological findings consistent with several other neurodegenerative conditions. Indeed, there are several neuropsychiatric conditions that can result in abnormal tau deposition within the brain, including normal aging, substance abuse, and psychiatric illnesses (Solomon & Zuckerman, 2014). As such, further research is needed to better delineate these conditions and fully examine the risk factors associated with repetitive head trauma and the developmental of neurodegenerative illness.

The current study also sought to examine the relationship between diffusivity metrics and neuropsychological tests of processing speed, attention, and executive function, given that these are common complaints during the acute stages of concussion recovery. While a few cognitive measures were significant predictors of diffusivity measures across the entire sample during postseason scans, none met more conservative significance thresholds. Additionally, the directionality of two relationships between ROI diffusivity metrics and cognitive performance which were significant (namely the relationship between PASAT (2.0 second pacing) and FA values within the corpus callosum, as well as between WAIS-III Digit Symbol-Coding and MD values within the corpus callosum) were somewhat counterintuitive. This finding could have several explanations, including a lack of relationship between these metrics and neuropsychological measures, idiosyncratic differences between participants but not at group levels, or lack of adequate sensitivity in current neuropsychological assessments to detect any consequences of subclinical anatomical changes stemming from repeated HIE. However, if taken at face value, there does appear to be emerging evidence to suggest potential utility of both the PASAT and Category Fluency subtest of the D-KEFS, as these tests emerged most frequently across several ROIs.

The lack of differences in diffusivity measures between the two groups at pre-season may have several short- and long-term implications. Given the assumption that these division I athletes have been involved in athletic participation for at least several years prior to their participation in the study, the lack of measurable differences may suggest a natural and spontaneous recovery process occurring during periods of time where HIEs are not prevalent (i.e., the offseason). This idea has been advanced by Mayinger and colleagues (2018) who found that previous observed differences in white matter integrity present between pre- and post-season scans normalized following a 6-month period in which no additional HIEs occurred. This finding, replicated in the current study, is reassuring given current scrutiny surrounding potential short- and long-term effects of repetitive head impacts. It is possible that, while pre-season values are not statistically different, some persistent injury has nevertheless occurred and may accumulate over time; however, longitudinal research has not yet addressed this concern. The efficacy of rest, with its possible associated recovery, represents a vital future research direction, as no evidence-based recommendations surrounding an appropriate period of non-contact rest have yet been delineated.

There are several limitations of the current study. First, DTI image registration, physiologic motion, and inherent noise during scans limit the precision with which DTI techniques can generate clinically relevant conclusions. While these factors were considered, and estimated subject motion was included as a covariate within all models, limits on precision remain. Furthermore, data collection occurred in 2007–2011, creating potential generalizability limitations in using an older dataset. Admittedly, evolution in helmet-based impact tracking has occurred and there are limits to analytical methods used to reconstruct impact trajectories using two gyroscopes (see Wilcox, 2014). However, utilized imaging methods are believed to be consistent with current guidelines and are not expected to introduce biases, mitigating these concerns. Additionally, this sample may not be generalizable to all other athlete populations, including professional or youth athletes, due to differences in brain maturity, differing history and magnitude of impact exposure, and physical strength. A better understanding of these factors and a greater understanding of potential consequences of concussions in different cohorts will allow establishment of more appropriate return-to-play guidelines. Additionally, due to sample size discrepancies between males and females, gender was not included within utilized statistical models. Although our sample is reasonably large, it covers a heterogeneous sample of sports and sexes; this breadth limits our ability to model more fine-grained details such as those between sports or between sexes. Future studies with larger samples would provide an opportunity to focus on sex differences not modeled in the current work.

Finally, while the results of the current study do include isolated findings with statistical significance, it would be inappropriate to draw blanket conclusions, including attempts to identify at-risk athletes for future cognitive decline, at the present time. This is partially due to the nature of the GEE approach, which explicitly models average rather than participant-level effects. Future research is necessary to continue to expand our understanding of the effects of HIE in athletic settings and to develop prospective and longitudinal experimental designs that can better delineate the clinical significance of any effects. The current findings contribute to and expand our knowledge of anatomical and cognitive changes over the course of a single season in contact athletes, and underscore the importance of considering methodology when interpreting findings in this population, as differing image analysis techniques may lead to different conclusions regarding significant effects.

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Table 1:

Sample demographic characteristics

	Total Sample	Contact Athletes	Non-Contact Athletes		
		Mean (SD)		t	p
Age	19.29 (1.27)	19.07 (1.20)	19.51 (1.30)	2.18	.031
WRAT-4 Word Reading SS	114.77 (10.58)	112.08 (10.71)	117.32 (9.87)	3.16	.002
Variable		N (% of sample)		χ^2	p
Sex				1.72	.190
Male	116 (75.3%)	60 (80.0)	56 (70.9)	---	---
Female	38 (24.7%)	15 (20.0%)	23 (29.1)	---	---
Handedness				2.40	.122
Right	141 (91.6)	66 (88.0)	75 (94.9)	---	---
Left	13 (8.4)	9 (12.0)	4 (5.1)	---	---
Sport Classification					
Men's Hockey	9 (5.8)	9 (12.0)	---	---	---
Football	51 (33.1)	51 (68.0)	---	---	---
Cross Country	43 (27.9)	---	43 (54.4)	---	---
Rowing	31 (20.1)	---	31 (39.2)	---	---
Golf	4 (2.6)	---	4 (5.1)	---	---
Women's Hockey	15 (9.7)	15 (20.0)	---	---	---
Tennis	1 (0.6)	---	1 (1.3)	---	---
Visit Classification *				0.63	.731
Preseason Scan	136 (49.6)	58 (48.3)	78 (50.6)	---	---
Postseason Scan	123 (44.9)	54 (45.0)	69 (44.8)	---	---

* Percentages may not equal 100% due to inclusion of mid-season scans

Note: Contact Athlete N = 75, Non-Contact Athlete N = 79

SD = Standard Deviation; SS = Standard Score; WRAT-4 = Wide Range Achievement Test, 4th Edition

Table 2:

Region of interest differences in diffusivity measures across pre- and postseason scans in contact athletes

ROI	Measurement	Effect	Adjusted p value
Corpus Callosum	FA	−2.54E-03 (p = .501)	> 0.99
	MD	+2.14E-06 (p = .630)	> 0.99
Anterior Thalamic Radiations	FA	−1.93E-03 (p = .694)	> 0.99
	MD	+7.57E-06 (p = .169)	0.68
Cingulum	FA	−2.76E-03 (p = .739)	> 0.99
	MD	+1.06E-05 (p = .065)	0.26
Uncinate Fasciculus	FA	−9.73E-05 (p = .986)	> 0.99
	MD	+1.30E-05 (p = .031)	0.12

Note: Interpretations of statistical significance were subjected to Bonferroni-corrected alpha thresholds (see text). Negative effect directions represent a measurement decrease, while positive effect directions represent a measurement increase.

FA = Fractional Anisotropy; MD = Mean Diffusivity; ROI = Region of Interest

Table 3:

Relationship between HIE variables and postseason diffusivity differences in contact athletes

Predictor	ROI	Effect		Adjusted p value
Season Hit Frequency	Corpus Callosum	FA	+1.48E-06 (p = .744)	> 0.99
		MD	−8.30E-10 (p = .854)	> 0.99
	Anterior Thalamic Radiations	FA	−5.03E-06 (p = .258)	> 0.99
		MD	−1.39E-10 (p = .981)	> 0.99
	Cingulum	FA	−1.28E-05 (p = .117)	> 0.99
		MD	+1.87E-09 (p = .753)	> 0.99
	Uncinate Fasciculus	FA	+4.16E-06 (p = .439)	> 0.99
		MD	+6.83E-09 (p = .403)	> 0.99
Season Linear Acceleration	Corpus Callosum	FA	−1.39E-04 (p = .066)	> 0.99
		MD	+1.27E-07 (p = .228)	> 0.99
	Anterior Thalamic Radiations	FA	−2.94E-06 (p = .981)	> 0.99
		MD	+1.99E-07 (p = .088)	> 0.99
	Cingulum	FA	−7.46E-05 (p = .722)	> 0.99
		MD	+1.99E-07 (p = .089)	> 0.99
	Uncinate Fasciculus	FA	−2.03E-05 (p = .862)	> 0.99
		MD	+3.14E-07 (p = .018)	0.29
Season Rotational Acceleration	Corpus Callosum	FA	−1.90E-06 (p = .219)	> 0.99
		MD	+1.85E-09 (p = .402)	> 0.99
	Anterior Thalamic Radiations	FA	+3.72E-07 (p = .888)	> 0.99
		MD	+4.12E-09 (p = .091)	> 0.99
	Cingulum	FA	−1.64E-06 (p = .710)	> 0.99
		MD	+4.07E-09 (p = .114)	> 0.99
	Uncinate Fasciculus	FA	+3.30E-07 (p = .891)	> 0.99
		MD	+6.72E-09 (p = .017)	0.27
Season HITsp	Corpus Callosum	FA	−1.63E-04 (p = .197)	> 0.99
		MD	+1.72E-07 (p = .351)	> 0.99
	Anterior Thalamic Radiations	FA	+5.44E-05 (p = .809)	> 0.99
		MD	+3.15E-07 (p = .126)	> 0.99
	Cingulum	FA	−1.86E-04 (p = .630)	> 0.99
		MD	+3.67E-07 (p = .103)	> 0.99
	Uncinate Fasciculus	FA	+6.83E-06 (p = .974)	> 0.99
		MD	+5.42E-07 (p = .021)	0.34

Note: Interpretations of statistical significance were subjected to Bonferroni-corrected alpha thresholds (see text). Negative effect directions represent a measurement decrease, while positive effect directions represent a measurement increase.

FA = Fractional Anisotropy; HIE = Head Impact Exposure; MD = Mean Diffusivity; ROI = Region of Interest

Table 4:

Relationship between significant cognitive variables and postseason diffusivity differences across the entire sample

ROI	Cognitive Test		Effect	Adjusted p value
Corpus Callosum	CPT Stimulus Response Time	FA	+7.68E-05 (p = .045)	0.41
	CPT Distractor Response Time	FA	+8.33E-05 (p = .027)	0.24
	PASAT B	FA	−4.33E-04 (p = .047)	0.42
	WAIS-III Digit Symbol-Coding	MD	+3.27E-07 (p = .020)	0.18
	D-KEFS TMT Condition 4	MD	−2.31E-07 (p = .021)	0.19
Anterior Thalamic Radiations	D-KEFS Category Fluency	FA	−6.26E-04 (p = .008)	0.07
Cingulum	D-KEFS Category Fluency	FA	−1.74E-03 (p = .014)	0.13
	D-KEFS Sorting Total Recognition	FA	−5.48E-04 (p = .028)	0.25
	PASAT B	FA	−1.12E-03 (p = .050)	0.45
	PASAT D	FA	−2.20E-03 (p = .038)	0.34
	PASAT D	MD	+6.23E-07 (p = .025)	0.25
Uncinate Fasciculus	D-KEFS Category Fluency	MD	+5.02E-07 (p = .020)	0.18
	PASAT B	MD	+6.87E-07 (p = .017)	0.15
	PASAT D	MD	+6.60E-07 (p = .025)	0.23

Note: Interpretations of statistical significance were subjected to Bonferroni-corrected alpha thresholds (see text). Negative effect directions represent a measurement decrease, while positive effect directions represent a measurement increase.

CPT = Gordon Continuous Performance Test; D-KEFS = Delis-Kaplan Executive Function System; FA = Fractional Anisotropy; MD = Mean Diffusivity; PASAT = Paced Auditory Serial Addition Test; ROI = Region of Interest; TMT = Trail Making Test