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## ABSTRACT

**Objective:** To determine whether exposure to repetitive head impacts over a single season affects white matter diffusion measures in collegiate contact sport athletes.

**Methods:** A prospective cohort study at a Division I NCAA athletic program of 80 nonconcussed varsity football and ice hockey players who wore instrumented helmets that recorded the acceleration-time history of the head following impact, and 79 non-contact sport athletes. Assessment occurred preseason and shortly after the season with diffusion tensor imaging and neurocognitive measures.

**Results:** There was a significant ($p = 0.011$) athlete-group difference for mean diffusivity (MD) in the corpus callosum. Postseason fractional anisotropy (FA) differed ($p = 0.001$) in the amygdala (0.238 vs 0.233). Measures of head impact exposure correlated with white matter diffusivity measures in several brain regions, including the corpus callosum, amygdala, cerebellar white matter, hippocampus, and thalamus. The magnitude of change in corpus callosum MD postseason was associated with poorer performance on a measure of verbal learning and memory.

**Conclusion:** This study suggests a relationship between head impact exposure, white matter diffusion measures, and cognition over the course of a single season, even in the absence of diagnosed concussion, in a cohort of college athletes. Further work is needed to assess whether such effects are short term or persistent. ***Neurology*® 2014;82:63–69**

## GLOSSARY

**AD** = axial diffusivity; **CVLT-II** = California Verbal Learning Test-II; **DTI** = diffusion tensor imaging; **DWI** = diffusion-weighted imaging; **FA** = fractional anisotropy; **GEE** = generalized estimating equation; **HIE** = head impact exposure; **MD** = mean diffusivity; **NEX** = number of excitations; **ROI** = region of interest; **TBI** = traumatic brain injury; **TE** = echo time; **TR** = repetition time; **WRAT-4** = Wide Range Achievement Test-4.

There is growing concern that head impacts sustained while playing contact sports may lead to a variety of worrisome outcomes, including increased susceptibility to concussion, long-term cognitive decline, and chronic traumatic encephalopathy.[1–4]

Studies of repetitive impacts not associated with diagnosed concussion are few and contradictory. One study reported abnormal cognitive indices in season and postseason,[5] while another showed postseason cognitive improvements, probably related to practice effects.[6] Our group[7] failed to find large *group* differences in cognition at postseason assessments in collegiate contact sport athletes; however, a significantly higher percentage of the contact sport group showed worse-than-predicted postseason performance on a test of verbal learning, suggesting that a subgroup of athletes are vulnerable to the cognitive effects of repetitive head impacts.

Diffusion-weighted imaging (DWI) methods have been used to probe white matter integrity, particularly in mild and moderate traumatic brain injury (TBI).[8–10] In athletes, work has focused on individuals with concussions. For example, in a study of 10 concussed college students studied with diffusion tensor imaging (DTI),[11] the concussed group showed elevated mean diffusivity (MD) in the left inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. In another report,[12] concussed football players studied 1 week and 6 months after injury had elevated

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fractional anisotropy (FA) and axial diffusivity (AD) in some brain regions (e.g., corpus callosum). However, another study[13] found no differences in FA or MD in college athletes 1 month after concussion. Few publications focus on the effects of repetitive head impacts in athletes without concussion.[14]

This study tested the hypothesis that participation in a season of a contact sport in the absence of a diagnosed concussion is associated with changes in white matter diffusion measures and that the degree of change is correlated with head impact exposure (HIE) and cognitive performance.

## METHODS

**Participants.** Two athlete cohorts enrolled between 2007 and 2011 at Dartmouth College underwent preseason and postseason neuroimaging. The contact sport cohort consisted of football players and ice hockey players (men and women). The non–contact sport cohort consisted of varsity athletes on a variety of teams, including track, crew, and Nordic skiing. Study participation was offered to all members of these contact and noncontact teams. We excluded athletes with a history of concussion during the index season, significant systemic medical illness, or current psychiatric disorders. For the non–contact sport cohort, we also excluded those with self-reported prior concussion. Some participants were also included in our previous report of the cognitive effects of repetitive head impacts.[7]

**Standard protocol approvals, registrations, and patient consents.** The protocol was approved by the institutional review board at Dartmouth and all participants gave written informed consent.

**Imaging methods.** Scans were acquired on a research-dedicated 3T Philips Achieva magnet. This 3.0T system has the high-performance Quasar Dual gradient set with strengths up to 80 mT/m and slew rates up to 200 T/m/second and an anatomical landmark–based longitudinal repositioning system (SameScan/SmartScan). A Philips 8-channel SENSE head coil was used.

**Diffusion-weighted imaging.** DWI was carried out using 46 diffusion directions (b = 1,000 seconds/mm$^2$), optimized via electrostatic repulsion to achieve a homogeneous distribution over a sphere,[15] plus one volume without diffusion gradients (b = 0). The imaging resolution was $2 \times 2 \times 2$ mm$^3$, echo time (TE) was 76 ms, repetition time (TR) was specified as "shortest" (roughly 8,100–8,600 ms), number of excitations (NEX) = 1, and SENSE factor = 2.5. DWI acquisition time was 8.1 minutes. Calculation of tensors was carried out using ExploreDTI v. 4.8.2,[16,17] using the RESTORE algorithm[18] plus optional processing for correction of bulk motion.

FA and MD were chosen as our primary diffusivity measures. Both FA and MD give an indication of axonal function and are potential injury biomarkers. While AD and radial diffusivity have been reported in the TBI literature and can be interpreted as markers of axonal integrity (e.g., reference 14), they have been shown to be difficult to interpret in areas of crossing fibers and other complex architectures.[19] Prior to data analysis, we identified the corpus callosum as our primary region of interest (ROI) based on the density of long white matter tracts and previous work showing vulnerability of this region to diffuse axonal injury, which is often assumed to underlie the effects of mild TBI/concussion.[20] Six additional brain regions were chosen for planned secondary analyses: cerebral white matter, brainstem, thalamus, hippocampus, amygdala, and cerebellar white matter.

**Anatomic reference.** An MPRAGE (magnetization-prepared rapid acquisition with gradient echo) T1-weighted sequence was used in each session with the following parameters: 140 contiguous 1.2-mm sagittal slices, TR: 6.8 ms, TE: 3.3 ms, inversion time: 852.9 ms, turbo field echo prepulse delay: shortest, flip angle: 8°, NEX: 1, bandwidth/pixel: 241, field of view: 256 mm, matrix 256, $1.0 \times 1.0$ mm in-plane resolution. This series balances scan time, signal-to-noise ratio, high gray/white tissue contrast, and high spatial resolution (scan duration: 8:55 minutes).

**Subject-specific ROI analysis.** FreeSurfer[21] was used to carry out a subcortical segmentation of each subject's anatomic reference scans and to create the preselected ROIs. To maximize the expected accuracy and eliminate any session bias in the ROIs, FreeSurfer's longitudinal stream[22] was employed to create a longitudinally unified template space and label image[23] for each subject using a robust registration.[24] For each DTI scan, SPM5's coregistration function was used to realign the skull-stripped FreeSurfer unified anatomy image for the subject to the skull-stripped b = 0 diffusion image for the session, and to apply the same transformation to propagate the subjects' label maps to that DTI scan space. Default SPM5 settings were used except for the specification of nearest neighbor interpolation to preserve label values.

**Imaging quality control.** Quality assessments consisted of a combination of manual review of diffusion images and tests in ExploreDTI and MATLAB v. R2010b/7.11 based on reference 17. Of the 287 scans acquired, 10 helmet athlete scans were unusable due to scanner configuration issues, 1 scan failed quality checks, and a further 4 scans could not be successfully processed in ExploreDTI, resulting in 272 usable scans.

**Assessment of cognition.** Participants completed a 2.5-hour battery of standardized neuropsychological tests at both time points. As in our previous work,[7] the California Verbal Learning Test-II (CVLT-II) Total Acquisition Trials 1–5[25] was chosen as the primary cognitive outcome measure and the Wide Range Achievement Test-4 (WRAT-4) reading test was used as a proxy for general intelligence.

**Biomechanical measurements.** Study participants wore helmets instrumented with HIT System technology (Riddell, Inc., Rosemont, IL; Simbex, Lebanon, NH) to record HIE during all team-organized practices and games. This technology has been described previously in the literature, including detailed descriptions of its development,[26,27] measurement accuracy,[28,29] and on-field performance.[29–31] In brief, instrumented helmets are fitted with a modified helmet liner that positions an array of 6 single-axis accelerometers against the head to enable in vivo head acceleration measurement (see figure 1). If any accelerometer exceeds a team-established threshold (14.4*g* in this study), 40 ms of data (8 ms pretrigger and 32 ms posttrigger) are recorded and transmitted wirelessly to a sideline laptop computer. Accelerometer data are then processed using a simulated annealing algorithm to solve for acceleration at the head center of gravity. Prior to data analysis, 4 biomechanical variables were chosen as representative indicators of HIE for each player: number of head impacts, the 95th percentile peak linear acceleration, the 95th percentile peak rotational acceleration, and the 95th percentile HITsp (derived from peak acceleration, impact duration, and impact location). Two time

**Figure 1** Accelerometer locations within the instrumented football and hockey helmets

Accelerometer locations (indicated by red circles) within the instrumented football and hockey helmets record acceleration at 6 locations on the head. Raw acceleration data for each recorded event are processed using an optimization algorithm to obtain linear and rotational acceleration about the head center of gravity.

epochs were chosen to capture both cumulative effects of a season of HIE ($H_{season}$) and effects of recent HIE ($H_{recent}$). Such an approach takes into account that directional change in white matter metrics can vary as a function of the interval from the precipitating injury and variation across subjects in the end-of-season to postseason imaging interval.[7,10,32,33]

**Statistical analyses.** Distributions for cognitive performances and HIE were examined for outliers and distributional characteristics. Comparison of contact and non–contact sport athletes used means and $t$ tests for continuous variables and $\chi^2$ tests for categorical variables with respect to basic demographic information.

**Contact vs noncontact athlete comparisons.** Two generalized estimating equation (GEE) models were used to test the hypothesis that contact sport and non–contact sport athletes differed significantly with respect to the diffusivity outcome measures (FA and MD). The models included visit type (preseason vs postseason), age, WRAT-4 reading score, scanner epoch (accounts for potentially significant changes in the scanner environment, such as scanner upgrades over the 4-year course of the study), and subject motion (using motion parameters generated by ExploreDTI in its affine-based motion correction).

**Evaluation of biomechanics predictors in contact sport athletes.** To assess for relationships between HIE variables and diffusivity measures, 2 related GEE models were used (FA and MD). These models used the contact athletes only and included the 4 prespecified biomechanical variables assessed over the 2 time frames (season and 14 days prior to postseason scan).

**Evaluation of functional significance of diffusivity measures.** To characterize relationships between diffusivity measures and cognitive function, we assessed the correlation between postseason diffusivity measures and the CVLT-II,[25] a test of verbal learning and memory using a regression-based $z$ score approach.[7,34] The noncontact athlete data were used to establish a predicted range of postseason performance; $z$ scores representing change (preseason to postseason) for the CVLT-II were computed using multiple regression analysis with adjustment for test-retest interval and WRAT-4 reading score. As in our prior work,[7] a value of $z < -1.5$ (i.e., follow-up test scores 1.5 or more SDs lower than the predicted value) served as an indicator of significantly poorer-than-expected postseason performance. Clinically, this represents a meaningful change in an individual relative to his or her own baseline or a clinically significant impairment relative to normative data (a decline of this magnitude is expected in less than 7% of the normal population).

## RESULTS

**Participants.** Results include 272 scans from 159 athletes (123 scans of 80 contact sport athletes and 149 scans of 79 non–contact sport athletes). Not all subjects returned for postseason scans. Five contact sport athletes were dropped from the postseason analysis because they sustained a concussion during the season. The proportion of subjects who returned for postseason scans was similar across groups: 88% of noncontact controls and 83% of contact sport athletes. Table 1 summarizes demographic variables for the contact and noncontact athletes. The 2 groups showed statistically significant differences in age ($p = 0.013$) and in WRAT-4 reading ($p < 0.001$). Although neither difference is clinically meaningful, these variables were included as covariates in the GEE models. Athletes with and without matched preseason and postseason assessments did not differ with respect to age, sex, handedness, or preseason CVLT-II scores.

**Head impact exposure.** Descriptive statistics for the number of head impacts sustained and the player-specific 95th percentile peak linear acceleration, peak rotational acceleration, and HITsp are summarized in table 1. As noted, HIE measures were aggregated over a single season of play as well as within 14 days of the postseason scan.

**Imaging.** There was a main effect of athlete group ($p = 0.036$) for MD in the corpus callosum (see figure 2). In addition, postseason FA and MD differed across groups in the amygdala ($p < 0.001$, $p = 0.042$). There were no other significant differences in FA or MD, including differences between preseason and postseason time points in either group.

**Relationship of head impacts and white matter metrics.** For each HIE measure, season values were tested with and without recent values as covariates. Table 2 summarizes the findings. There was a significant association between head impact metrics and postseason white matter measures in a number of regions, including the corpus callosum (number of hits during the prior 14-day window), amygdala (seasonal 95th percentile rotational acceleration and HITsp), cerebellum (hits over both the entire season and the 14-day window, seasonal and recent 95th percentile linear and rotational acceleration, and seasonal 95th percentile HITsp), and hippocampus (hits over the entire season and 95th percentile linear and rotational accelerations over the recent 14-day window).

**Table 1** Demographics and head impact exposure (HIE) for the season and within 14 days of postseason scan

| | Noncontact | Contact[a] |
|---|---|---|
| **Age** | | |
| Mean (SD) | 19.5 (1.3) | 19.0 (1.1) |
| Range | 18–22 | 18–22 |
| **Sex** | | |
| Male | 56 | 64 |
| Female | 23 | 16 |
| **Handedness** | | |
| Right | 75 | 71 |
| Left | 4 | 9 |
| **WRAT-4 reading (scaled score)** | | |
| Mean (SD) | 117.5 (9.7) | 111.5 (10.2) |
| Range | 96–142 | 92–142 |
| **CVLT-II (preseason): 65 contact, 79 noncontact** | | |
| Mean (SD) | 59.2 (7.1) | 58.0 (8.1) |
| Range | 44–74 | 31–77 |
| **CVLT-II (postseason): 58 contact, 70 noncontact** | | |
| Mean (SD) | 62.6 (8.3) | 59.3 (8.0) |
| Range | 33–76 | 39–76 |
| **Number of impacts (season HIE)** | | |
| Mean (SD) | | 503 (419) |
| Range | | 9–2,046 |
| **Number of impacts (14-day HIE)** | | |
| Mean (SD) | | 20.2 (47) |
| Range | | 0–240 |
| **Linear acceleration (95th) (season HIE)** | | |
| Mean (SD) | | 54.8 (11.4) |
| Range | | 33.4–88.3 |
| **Linear acceleration (95th) (14-day HIE)** | | |
| Mean (SD) | | 18.5 (26.9) |
| Range | | 0–90.4 |
| **Rotational acceleration (95th) (season HIE)** | | |
| Mean (SD) | | 2,552 (635) |
| Range | | 1,481–4,540 |
| **Rotational acceleration (95th) (14-day HIE)** | | |
| Mean (SD) | | 954 (1,455) |
| Range | | 0–5,548 |
| **HITsp (95th) (season HIE)** | | |
| Mean (SD) | | 30 (7.2) |
| Range | | 16.9–52.9 |
| **HITsp (95th) (14-day HIE)** | | |
| Mean (SD) | | 10.5 (15.8) |
| Range | | 0–60.9 |

Abbreviations: CVLT-II = California Verbal Learning Test-II; WRAT-4 = Wide Range Achievement Test-4.
The 2 groups do not differ on CVLT-II at preseason ($t = 0.90$, $p = 0.37$), but they do differ at postseason ($t = 2.27$, $p = 0.025$).
[a] HIE applicable to contact athletes only.

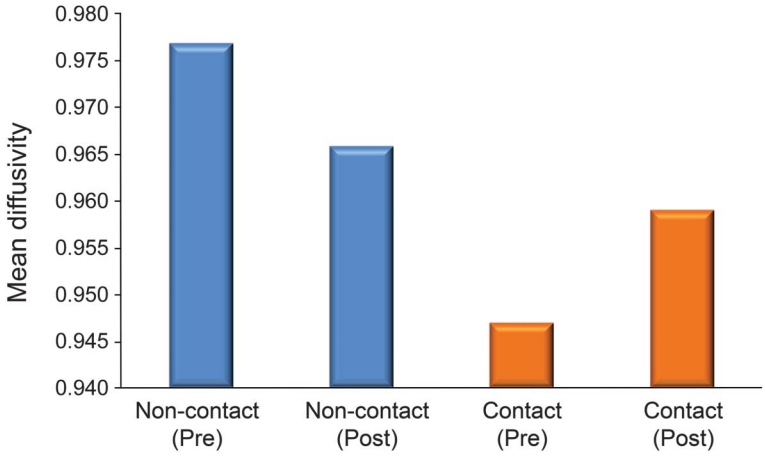
**Relationship of postseason cognitive performance to white matter metrics.** A subgroup of the athletes (contact 20% vs noncontact 11%) performed worse than predicted (defined by scores >1.5 SDs below the predicted score) at the postseason assessment on the CVLT-II. This group showed more change in MD in the corpus callosum ($p = 0.017$) relative to the normally performing group of athletes, but did not differ meaningfully from the remainder of the group in other respects (table 3).

**DISCUSSION** This large prospective cohort study suggests there are differences in white matter diffusion metrics between college contact and non–contact sport varsity athletes when studied across a single season. Furthermore, the relationship between head impact measures and white matter diffusion measures suggests a causal relationship between the magnitude and timing of head impacts and change in white matter measures in some brain regions. The observation that the group with poorer-than-predicted postseason performance on a measure of verbal learning and memory had higher changes in diffusivity measures (MD) in the corpus callosum suggests that the observed white matter changes may have some functional significance.

It is important to emphasize that our cohort of contact sport athletes were not diagnosed with a concussion during the index season. Not surprisingly, the absolute magnitude of the group differences, although statistically significant, is small, and less than what has been reported in the literature for clearly defined TBI. For example, one study of 57 moderate and 26 mild TBIs 5–14 days postinjury showed differences of approximately 0.06 in corpus callosum FA between controls and the TBI group.[33] Another study of 60 individuals with mild TBI and 34 controls found a nonsignificant difference of 0.001 for FA in the genu of the corpus callosum 6–8 weeks postinjury and an MD difference in the splenium of the corpus callosum, which was 0.781 for TBIs vs 0.767 for controls (0.014 difference, $p = 0.050$).[35] Direct comparisons of DTI measures for nonconcussed athletes have not been reported previously, to our knowledge.

There are several limitations to this study worth noting. The reproducibility of FA and MD in DTI is sufficient to track relatively small changes longitudinally in a single subject,[36] but subject bulk and physiologic motion, image registration, and inherent noise combine to make assessing the precision with which comparisons can be made in any individual case difficult. Although this is a large sample, it is drawn from a single setting and thus may not be representative of other athlete populations, such as professional athletes or youth populations, due to differences in brain maturity, neck strength, training,

**Figure 2** Mean diffusivity values for the corpus callosum of noncontact and contact athletes preseason and postseason




Examination of the mean diffusivity values for the corpus callosum of noncontact and contact athletes preseason and postseason indicates a main effect of athlete group ($p = 0.036$).

and exposure metrics. Although it is common to ascribe changes in diffusion metrics to abnormalities in "white matter integrity," what this actually means and its functional significance have not been fully established. We believe our findings are consistent with a link between white matter diffusion measures, HIE, and cognition, but there is significant variability among the athletes. It would be premature at this point to use these techniques to identify individual at-risk athletes.

**Table 2** Association of HIE and postseason FA or MD

| ROI | Predictor | Effect |
|---|---|---|
| **Corpus callosum** | Recent hits | MD −1.59E-04 ($p = 0.001$) |
| **Amygdala** | Season 95th HITsp | MD +4.38E-04 ($p = 0.019$) |
| | Season 95th linear | MD +1.99E-04 ($p = 0.050$) |
| | Season 95th rotation | MD +5.12E-06 ($p = 0.023$) |
| **Cerebellar white matter** | Season hits (w/recent) | FA +6.05E-06 ($p = 0.014$) |
| | Recent hits | FA −6.23E-05 ($p = 0.035$) |
| | Season 95th HITsp (w/recent) | FA +1.35E-04 ($p = 0.014$) |
| | Season 95th linear (w/recent) | FA +6.59E-05 ($p = 0.021$) |
| | Recent 95th linear | FA −7.90E-05 ($p = 0.022$) |
| | Season 95th rotation (w/recent) | FA +1.53E-06 ($p = 0.022$) |
| | Recent 95th rotation | FA −1.47E-06 ($p = 0.028$) |
| **Hippocampus** | Season hits | FA +4.52E-06 ($p = 0.025$) |
| | Season hits (w/recent) | FA +5.43E-06 ($p = 0.038$) |
| | Recent 95th linear | MD +2.29E-04 ($p = 0.046$) |
| | Recent 95th rotation | MD +4.62E-06 ($p = 0.033$) |

Abbreviations: FA = fractional anisotropy; HIE = head impact exposure; MD = mean diffusivity; ROI = region of interest.
Predictors tested were of 3 types: whole season values alone, whole season values controlling for recent values, and recent values (adjusted for whole season values).

Of note, we find neither preseason group differences nor large-scale, systematic differences across diffusion measures postseason. These findings are somewhat reassuring in the context of the recent concern about long- and short-term consequences of contact sports and recent reports of white matter changes in concussed athletes and retired National Football League players.[37] Furthermore, these athletes typically have been exposed to many prior seasons of repetitive head impacts, suggesting the possibility that season-induced changes may normalize during the off-season. This is consistent with the observation that thousands of individuals have played contact sports for many years without developing progressive neurodegenerative disorders.

Nevertheless, these findings suggest that some brain regions in some athletes are altered by repetitive impacts over the course of a season, even in the absence of diagnosed concussion, that the frequency and magnitude of the impacts can modulate these white matter changes, and that these changes may be related to verbal learning and memory. Adequate performance on the CVLT-II is best conceptualized as being subserved by a distributed circuitry with nodal points in bifrontal, medial temporal, and cerebellar cortices, along with attendant white matter connections.[38,39] Thus the finding of alterations in white matter metrics of medial temporal, cerebellar, and callosal regions (table 2) associated with a season of repetitive impacts is consistent with the CVLT-II findings.

It is also possible that our ability to detect subtle changes in white matter with current DTI technology may not be uniformly sensitive across all brain regions. For example, although some have postulated that triangulation of biomechanical forces to the upper brainstem and midbrain regions may generate the alteration of consciousness associated with concussive injury,[40] we did not find significant associations between biomechanical force parameters and changes in white matter metrics in the brainstem. It is also important to consider that TBI-related changes in white matter may vary as a function of the interval from injury to neuroimaging assessment. For example, some studies have reported elevated FA in some brain regions within days of injury, whereas studies with longer injury-to-imaging intervals (weeks or years) more typically have shown reduced FA.[7,10,32,33] In the event that individuals are getting repetitive head impacts, as in our cohort, some brain regions and white matter changes may be in different phases (diffusivity increasing in some regions, decreasing in others) depending on the time course of HIE and its relationship to the time of imaging. Our analytic approach, which looked at both season effects and recent (14-day) effects and covaried for imaging interval, was chosen in an effort to address these issues. Nevertheless, these

**Table 3** Comparison of the normal (n = 34) and low (n = 9) postseason RBZ-CVLT-II subgroups of the contact sport athletes

| | Low RBZ-CVLT-II group | Normal RBZ-CVLT-II group |
|---|---|---|
| **Age** | | |
| Mean | 19.7 | 19.0 |
| SD | 1.12 | 0.90 |
| Range | 18.3–21.4 | 18.2–21.3 |
| **Sex** | | |
| Male | 8 | 23 |
| Female | 1 | 11 |
| **Handedness** | | |
| Right | 6 | 30 |
| Left | 3 | 4 |
| **WRAT-4 reading** | | |
| Mean | 116 | 109 |
| SD | 15.1 | 8.7 |
| Range | 92–142 | 98–131 |
| **CVLT-II (postseason)** | | |
| Mean | 47.7 | 62.7 |
| SD | 6.6 | 6.4 |
| Range | 39–56 | 49–76 |
| **Corpus callosum MD (preseason)** | | |
| Mean | 0.95 | 0.95 |
| SD | 0.03 | 0.04 |
| Range | 0.91–1.01 | 0.88–1.05 |
| **Corpus callosum MD (postseason)** | | |
| Mean | 0.97 | 0.95 |
| SD | 0.03 | 0.04 |
| Range | 0.94–1.02 | 0.87–1.07 |

Abbreviations: CVLT-II = California Verbal Learning Test-II; MD = mean diffusivity; RBZ = regression-based *z* score; WRAT-4 = Wide Range Achievement Test-4.
The group of contact athletes who performed more poorly than predicted on the CVLT-II showed more change in MD in the corpus callosum ($p = 0.017$) relative to the normally performing group of athletes. Other than the expected postseason CVLT-II differences, there were no group differences in demographic variables.

time effects may be obscuring additional findings, and we cannot exclude the possibility that detrimental effects on white matter might be detected with a longer prospective design.

The observation that there is a subgroup of athletes with differential susceptibility to repetitive impacts raises the question of what underlying factors might account for this. Additional studies are warranted given the public health implications.

## AUTHOR CONTRIBUTIONS

Thomas W. McAllister: conception and design, analysis and interpretation of data, drafting of manuscript, obtaining funding, supervision. Dr. McAllister had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. James C. Ford: analysis and interpretation of imaging data, drafting of manuscript. Laura A. Flashman: conception and design, analysis and interpretation of data, drafting of manuscript, obtaining funding, supervision. Arthur Maerlender: conception and design, analysis and interpretation of data, drafting of manuscript. Richard M. Greenwald: conception and design, analysis and interpretation of data, critical revision of manuscript, obtaining funding, supervision. Jonathan G. Beckwith: analysis and interpretation of data, critical revision of manuscript, statistical analysis, technical support. Richard P. Bolander: analysis and interpretation of data, critical revision of manuscript, statistical analysis. Tor D. Tosteson: statistical design, analysis and interpretation of data, critical revision of manuscript, statistical analysis. John H. Turco: conception and design, critical revision of manuscript, supervision. Rema Raman: statistical analysis and interpretation of data, critical revision of manuscript. Sonia Jain: statistical analysis and interpretation of data, critical revision of manuscript.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## DISCLOSURE

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