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Longitudinal alteration of cortical thickness and volume in high-impact sports

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Keywords
- Structural brain development
- High-impact sports
- College football
- Cortical thickness and volume

Highlights
- This longitudinal study compares changes in brain structure between athletes playing high impact and low impact sports (collegiate tackle football vs. volleyball).
- Football athletes show a decreased rate of age-related cortical thinning compared to volleyball athletes.
- Changes in brain structure were related to the years of prior football exposure, concussion history, position-based concussion risk, and performance at baseline on the Sports Concussion Assessment Tool (SCAT).
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Abstract

Collegiate football athletes are subject to repeated head impacts. The purpose of this study was to determine whether this exposure can lead to changes in brain structure. This prospective cohort study was conducted with up to 4 years of follow-up on 63 football (high-impact) and 34 volleyball (control) male collegiate athletes with a total of 315 MRI scans (after exclusions: football n=50, volleyball n=24, total scans=273) using high-resolution structural imaging. Volumetric and cortical thickness estimates were derived using FreeSurfer 5.3’s longitudinal pipeline. A linear mixed-effects model assessed the effect of group (football vs. volleyball), time from baseline MRI, and the interaction between group and time. We confirmed an expected developmental decrement in cortical thickness and volume in our cohort (p<0.001).

Superimposed on this, total cortical gray matter volume (p = .03) and cortical thickness within the left hemisphere (p=.04) showed a group by time interaction, indicating less age-related volume reduction and thinning in football compared to volleyball athletes. At the regional level, sport by time interactions on thickness and volume were identified in the left orbitofrontal (p=.001), superior temporal (p=.001), and postcentral regions (p< .001). Additional cortical thickness interactions were found in the left temporal pole (p=.003) and cuneus (p=.005). At the regional level, we also found main effects of sport in football athletes characterized by reduced volume in the right hippocampus (p=.003), right superior parietal cortical gray (p<.001) and white matter (p<.001), and increased volume of the left pallidum (p=.002). Within football, cortical thickness was higher with greater years of prior play (left hemisphere p=.013, right hemisphere p=.005), and any history of concussion was associated with less cortical thinning (left hemisphere p=.010, right hemisphere p=.011). Additionally, both position-associated concussion risk (p=.002) and SCAT scores (p=.023) were associated with less of the expected volume decrement of deep gray structures. This prospective longitudinal study comparing football and volleyball athletes shows divergent age-related trajectories of cortical thinning, possibly reflecting an impact-related alteration of normal cortical development. This warrants future research into the underlying mechanisms of impacts to the head on cortical maturation.
1. Introduction

A growing body of evidence has raised concerns about repeated concussive and sub-concussive (high-velocity impacts that do not cause concussion) head impacts in athletes participating in high-impact sports such as American football, subsequently referred to simply as football in this text (H. Ling, Hardy, & Zetterberg, 2015; Manley et al., 2017). Football is among the most popular sports in the United States (Ham, Kruger, & Tudor-Locke, 2016). Some estimates suggest that collegiate football players average more than 14 significant head impacts per game (Crisco et al., 2010, 2011). Repeated head impacts may carry significant risks for players and have been linked to neuropsychological impairments that often persist years after injury (Bailes, Petraglia, Omalu, Nauman, & Talavage, 2013; Bazarian et al., 2014; Koerte et al., 2016; H. Ling et al., 2015; Moore et al., 2016). Sport-related head injuries may also put athletes at an increased risk for developing neurodegenerative diseases such as Alzheimer’s disease, amyotrophic lateral sclerosis (ALS), and chronic traumatic encephalopathy (CTE) later in life (Lehman, Hein, Baron, & Gersic, 2012; McKee et al., 2009; Stern et al., 2011).

Emerging evidence suggests that younger athletes may take longer to recover and may be more vulnerable than adults to the effects of a mild traumatic brain injury (mTBI) (Moore et al., 2016). By the time players reach the college level, they have typically already participated in full contact play for several years and experienced concussive and/or sub-concussive impacts. This exposure to high impact sports can result in demonstrable brain changes as early as high school (Abbas et al., 2015; Davenport et al., 2014; Svaldi et al., 2015; Talavage et al., 2014). Sustaining multiple head impacts at a young age could have a cumulative effect with the potential to change the trajectory of brain development and result in long lasting changes well into adulthood.

Dynamic changes in brain structure occur throughout development into early adulthood. Total brain size reaches about 90% of its adult size by five years of age (Dekaban & Sadowsky, 1978). Although the age of peak cortical thickness and volume is still debated, it is thought to reach its maximum before teenage years (Tamnes et al., 2017) and before enrollment in the present collegiate study. This period of cortical expansion is followed by progressive cortical thinning which continues throughout adolescence and adulthood (Giedd et al., 2009; Narvacan, Treit, Camicioli, Martin, & Beaulieu, 2017; Shaw et al., 2008; Tamnes et al., 2017; Wierenga, Langen, Oranje, & Durston, 2014). This developmental trajectory may reflect a number of underlying biological mechanisms including changes in dendritic arborization, ongoing synaptic pruning (Bourgeois & Rakic, 1993; Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011), and increases in intracortical myelination which continues into adulthood (Tamnes et al., 2017; Whitaker et al., 2016; Yakovlev & Lecours, 1967). Disruptions to these normative developmental trajectories may lead to adverse cognitive and behavioral outcomes later in life (Dennis & Thompson, 2013; Selemon & Zecevic, 2015).

Although moderate to severe traumatic brain injuries are often associated with pathological changes including thinning of the frontal and temporal lobes (Govindarajan et al., 2016; Merkley et al., 2008; Wilde et al., 2012), atrophy is not always observed and some studies of mTBI have shown increased thickness after injury (Dall’Acqua et al., 2017; Wang et al., 2014). Studies examining changes resulting from high impact sports, which are presumably even less severe,
have also shown mixed results (Sara Tremblay, Pascual-Leone, & Théoret, 2018). For instance, aging former athletes are likely to experience cortical atrophy (Sebastien Tremblay et al., 2013); however, studies in collegiate athletes suggest that either more thinning (Meier, Bellgowan, Bergamino, Ling, & Mayer, 2015), or less developmental thinning with age (Albaugh et al., 2015) may result from concussion exposure. Still other studies have found both cortical thickening and thinning in college athletes with a history of concussion (Churchill et al., 2016). These effects are likely to be moderated by a variety of factors including age, cumulative exposure to impacts, heterogeneity of impact type, and severity of injury.

Overall, brain-wide structural alterations resulting from high-impact sports are not well understood. To date, previous studies of sports-related changes in cortical structure have been either cross-sectional, or only measure changes resulting from one year of exposure to high impacts sports and are commonly limited in their sample size. To our knowledge, this is the first multi-year study tracking cortical thickness and volume change in football. This is important because a longitudinal design across multiple years of exposure could account for individual differences at baseline that would otherwise complicate interpretations from a cross-sectional study and could better assess the cumulative effects of impacts during the study. Here, we tracked 97 collegiate athletes with longitudinal MRI including follow-up of up to four years, collecting a total of 315 MRI scans. Male volleyball athletes were chosen as an active, athletic control due to the low-contact nature of play relative to other collegiate sports and their low incidence rate of concussion, with an athlete exposure (AE) rate of .03 relative to football’s AE of .53 per 1000 AEs (Pfister, Pfister, Hagel, Ghali, & Ronksley, 2016). The goal of this work is to determine whether exposure to high-impact sports alters the developmental trajectory of cortical thickness, as well as gray and white matter volumes.

2. Methods

2.1. Study Population

We prospectively enrolled 63 high-impact (football) and 34 low-contact (volleyball) college athletes (Figure 1). All procedures were in accordance with the Institutional Review Board and Health Insurance Portability and Accountability Act. Written informed consent was obtained for all participants. We only enrolled athletes in collegiate football or volleyball with no self-reported history of brain surgery, severe brain injury, or major neurologic, psychiatric, or substance abuse disorder. Subjects were not excluded if they had a prior concussion. All brain MRIs were evaluated for abnormalities by a neuroradiologist to exclude any clinically evident brain injury. The study was introduced to members of the team in conjunction with athletic trainers and all interested athletes were enrolled. Athletes underwent brain MRI at the start of each season, when possible within 24-96 hours after a concussion, and after the last season of sport participation. During the first year of this study, athletes underwent an additional imaging session at the end of their season.

Football athletes self-reported number and timing of prior concussions, the number of years of playing football before enrollment in the study, and a pre-first-season Standardized Concussion Assessment Tool (SCAT, versions 2 and 3) evaluation (McCrory et al., 2009). One football athlete did not provide their years of tackle football experience. The SCAT evaluation included the cognitive assessment, coordination, balance, and standardized assessment of concussion
portions of the SCAT 2/3 (McCrory et al., 2009). The maximum score for this SCAT assessment was 61. Higher SCAT score indicates better performance.

Figure 1. Study enrollment showing exclusion criteria and final sample size for longitudinal analysis. FB = football athletes, VB = volleyball athletes.

Each athlete had 1-8 MRI time-points spanning a maximum of four years. Incidences of concussion in football during the study period were identified by the athletic trainers. In total, 19 concussions occurred in 15 football athletes, three of whom had more than one concussion. None involved loss of consciousness. Excluding one athlete who did not return to play, mean return to play was 10.3 days. Median return to play was 10 days and that the minimum and maximum return to play was 5 and 31 days, respectively. Post-concussion MRI was captured for 13 of these 19 concussions among 12 football athletes, one of whom had two concussions with post-concussion MRI. In two of the other post-concussion MRI subjects, the first imaging time-point was post-concussion (one day and 13 days, respectively) without prior baseline imaging. There were two volleyball athletes that suffered concussions: one during volleyball, and the other incidental. Post-concussive imaging for these two volleyball athletes, consisting of two and three time-points, respectively, were not included in our main analyses in order to avoid having injury-related effects in our control cohort. A board and CAQ-certified neuroradiologist with eleven years of post-residency experience blindly examined all scans for incidental abnormalities, resulting in exclusion of five athletes (14 scans in total). One subject’s base image had a FreeSurfer registration error resulting in the exclusion of the remaining two of the subject’s three scans (one was a post-concussive volleyball scan already excluded).

Given the longitudinal nature of this analysis, we excluded subjects who had less than two scans in total and whose follow up scans were less than six months from their baseline exam. In total,
this resulted in the inclusion of 50 football and 24 volleyball athletes with 195 and 78 scans respectively (Figure 1).

2.2. Image Acquisition
Data was acquired using a 3T MRI scanner (GE MR 750, Milwaukee, WI, USA) and an 8-channel-receive head coil. We acquired two repetitions of a 3D T1-weighted axial (1mm isotropic, inversion recovery fast spoiled gradient echo Brain Volume Imaging (BRAVO), repetition time (TR) 7.9ms, echo time (TE) 3.1ms, number of excitations (NEX) 1, 5.1 minutes, TI 450ms, FOV 240cm, matrix size 240x240 (product reconstruction 256x256), 182 slices (1mm thickness), and receive bandwidth of +/- 32kHz.

2.3. Segmentation
Cortical reconstruction and volume segmentation was performed using the FreeSurfer longitudinal pipeline version 5.3 (Reuter, Rosas, & Fischl, 2012; http://surfer.nmr.mgh.harvard.edu/). Specifically, an unbiased within-subject template space and image (Reuter & Fischl, 2011; Reuter, Schmansky, Rosas, & Fischl, 2012) was created using robust, inverse consistent registration (Reuter, Rosas, & Fischl, 2010). Skull stripping, Talairach transforms, and atlas registration as well as spherical surface maps and parcellations were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter, Schmansky, et al., 2012). The bases (within-subject templates) were manually edited by improving skull stripping with additional manual delineation and adding control points to extend the gray-white segmented junction. This meticulous step was blind to subject identity and took 2-3 iterations of corrections and FreeSurfer reconstruction by two separate reviewers according to criteria fully documented in the supplement. The longitudinal time-points were constructed from these edited bases, and we performed a similar additional step of blinded manual editing. Finally, deep gray structures (thalami and hippocampi) were also blindly edited to improve precision. We performed a final blinded outlier detection step by two raters to confirm correct cortical parcellation. The full editing protocol is outlined in the supplementary materials. Scans with total volume or thickness measurements over three standard deviations from the mean across all scans were removed (one scan met these criteria).

Thickness and volume values were collected based on the Desikan/Killiany atlas. In total there were 155 volume segmentations and 68 cortical thickness segmentations. All cortical thickness segmentations were analyzed. Out of the 155 volume segmentations, 75 were assigned as white matter, 12 were assigned as deep gray, and 68 were assigned as cortical gray matter. Miscellaneous segmentations (i.e. ventricles, vessels, choroid-plexus, etc.) were not analyzed. Total volume estimates for each scan were separately combined by summation across cortical gray matter, deep gray, and white matter regions. Total left and right hemisphere cortical thickness measurements were extracted from FreeSurfer. See the supplementary materials for the full ROI assignments.

2.4. Statistics
A linear mixed-effects model in Matlab (version 2016b) examined changes in thickness and volume. Results were verified using the package Stata (v15.0; StataCorp LP, College Station, TX; http://www.stata.com). Each model evaluated the effect of time (i.e. time from baseline scan), group (i.e. football or volleyball, football coded as 1; volleyball 0), and group by time
interaction. Estimated total intracranial volume (eTIV) and the age at the time of the baseline scan were included as covariates to account for any baseline differences in age and total brain size between groups. Subject identity was included as the within subject random effect. Demographic variables were analyzed using Wilcoxon rank sum and Fisher’s exact tests (Table 1). Race did not significantly contribute to any model by a likelihood ratio test. BMI similarly did not contribute to total volume effects. Although BMI did contribute to left hemisphere total thickness models, the key result of the interaction between group and time remained significant after its inclusion as a covariate. For consistency and simplicity across tests, the final model for all tests with both sports (both volume and thickness) included time, group, group by time interaction, eTIV, and age at baseline.

The model was first applied to whole brain volume and cortical thickness to look for
1. baseline shifts in the temporal trajectories between sports (the effect of group that is stable over time)
2. temporal trajectories common to both sports (the effect of time), and
3. differences in the temporal trajectories between sports (the interaction effect between group and time).

We first examined global (whole brain) then hemisphere and tissue-specific metrics, specifically:
a) total brain volume
b) left and right hemisphere cortical thickness, as well as total cortical gray matter volume, total white matter volume and total deep gray volume.
c) For significant effects in global metrics, we then applied the same model at the regional level to better localize where these effects are statistically significant on a region-by-region basis.

For regional level analyses, resulting p-values for each effect (i.e., separately for main effects and interactions) were considered statistically significant if they passed a Benjamini Hochberg false discovery rate (FDR) (Benjamini & Hochberg, 1995) adjusted threshold of p < .05 (q < .05). To further confirm the significance of these effects, we also applied an additional, more conservative, multiple correction technique developed by Li and colleagues (Lee et al., 2010; Li & Ji, 2005), which limits the family-wise error rate by estimating the number of independent comparisons. Assumptions of independence are derived from the eigenvalues of a correlation matrix between each dependent measure (i.e. ROI x ROI correlation matrix). The Li p value threshold was p = .0008 for volume and p = .0017 for thickness. Both FDR and Li corrections were performed separately across cortical volume (gray/white/deep gray) and thickness (left and right hemisphere) segmentations.

2.5. Within-football analyses
Next, we performed within-football analyses to evaluate four different possible covariates of interest: years of prior football exposure, the presence of concussion, the player position, and their SCAT score.

Prior football exposure: Football athletes had between 4 and 14 years of prior experience playing tackle football before their baseline MRI. A mixed effects model tested if cortical thickness and volume measurements was related to total years of football experience prior to study enrollment
or the interaction between total years of football experience and time after baseline MRI, covarying intracranial volume and age at baseline MRI.

**Presence of concussion:** A binary variable was created encompassing whether players had experienced a within-study concussion or a concussion prior to study enrollment. This split the data within the football group to 26 players with no history of concussion (83 scans) and 24 subjects with a previous concussion (111 scans). Within the football group, a mixed effects model tested whether cortical thickness and volume was related to concussion history or the interaction between time after baseline MRI and concussion history, covarying intracranial volume and age at baseline MRI.

**Player position:** Next, we tested if impact risk based on player position was related to cortical thickness and volume. For this analysis we used literature values of HITsp for each player position as a measure of impact severity (Crisco et al., 2011). HITsp is a weighted composite measure that incorporates linear and rotational acceleration, impact duration, and impact location for each position. A similar mixed model was used for this analysis that tested whether HITsp or the interaction between HITsp and time after baseline scan was related to thickness and volume measures.

**SCAT:** Finally, we tested whether cortical thickness and volume was related to their SCAT score (McCrory et al., 2009). Within the football group, a mixed effects model tested whether cortical thickness and volume was related to SCAT score or the interaction between time after baseline MRI and SCAT score, covarying intracranial volume and age at baseline MRI.

3. **Results**

3.1. **Subject Demographics**
Age at baseline showed a minimal but statistically significant difference between football and volleyball athletes [mean age (standard deviation): football: 19.18(1.66) years, volleyball: 19.59(.948) years, Z(P)=5.44( <.001), see Table 1]. Body mass index (BMI) showed a significant difference between football and volleyball athletes [mean BMI (standard deviation): football: 29.76(3.85), volleyball: 23.48(2.11), Z(P)=11.52(<.001)]. As expected, years of prior tackle football experience was higher in football athletes Z(P)=-13.07(<.001). There were 16 out of 50 football and 2 out of 24 volleyball athletes who had prior concussions. Within football, there were no statistically significant differences in SCAT scores at baseline between athletes who did not or did have a history of prior concussion. Football and volleyball athletes had equivalently low rates of ADHD and learning disabilities. Proportionally more African Americans and fewer Caucasians played football compared to volleyball.
Table 1: Age at baseline MRI, body mass index, years of prior football experience, prior concussion history, and SCAT scores are shown with standard deviations, minimum and maximum scores. As well as incidence of ADHD, learning disabilities, and race. SCAT scores were compared within football only (between football athletes without prior concussion (left) and with prior concussion (right)). A Wilcoxon rank sum test was utilized for age, body mass index, years of prior football experience, number of athletes with prior concussions, and SCAT scores, while a Fisher’s exact test was performed for all other rows. ADHD = Attention deficit hyperactivity disorder. The one athlete with a learning disability had dyslexia.
### Table 2. Longitudinal evaluation of total brain volume as well as the partitions of cortical gray, white matter, and deep gray volume, in addition to left and right hemisphere cortical thickness. Bolded effects have a p < 0.05, uncorrected.

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Group Effect (volume/thickness difference in mm³/mm² between sports)</th>
<th>Time Effect (volume/thickness difference in mm³/mm² per year collapsing across sports)</th>
<th>Group by Time Interaction (volume/thickness difference in mm³/mm² per year between sports)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>Coefficient (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Total Brain Volume</td>
<td>0.0620</td>
<td>-1772.35 (-3634.38,887)</td>
<td>1.03E-10</td>
</tr>
</tbody>
</table>

### Table 3. Individual regions showing group effects and/or group by time interactions on thickness and volume. Bolded effects pass multiple comparison based on FDR correction and * indicates effects which also pass correction per Li et al. (2011).

#### Regional Level

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Group Effect (volume/thickness difference in mm³/mm² between sports)</th>
<th>Time Effect (volume/thickness difference in mm³/mm² per year collapsing across sports)</th>
<th>Group by Time Interaction (volume/thickness difference in mm³/mm² per year between sports)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>Coefficient (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Right Superior Parietal</td>
<td>8.91E-08</td>
<td>-1759.37 (-2404,-1114)</td>
<td>9.35E-09</td>
</tr>
<tr>
<td>Right Superior Parietal White Matter</td>
<td>0.0001</td>
<td>-1199.33 (-1808,-589)</td>
<td>0.0689</td>
</tr>
<tr>
<td>Right Hippocampus</td>
<td>0.0020</td>
<td>-296.63 (-484,-108)</td>
<td>0.0167</td>
</tr>
<tr>
<td>Left Pallidum</td>
<td>0.0042</td>
<td>142.33 (44,239)</td>
<td>0.4928</td>
</tr>
<tr>
<td>Left Post Central</td>
<td>0.0272</td>
<td>-677.02 (-1277,-76)</td>
<td>4.478E-13</td>
</tr>
<tr>
<td>Left Lateral Orbitofrontal</td>
<td>0.2797</td>
<td>-192.49 (-541,156)</td>
<td>3.247E-13</td>
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<tr>
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### 3.2. The effect of sport (group main effect)

**Whole brain level:** Total brain volume showed a trend towards being lower in football compared to volleyball (main effect of group: β = -17723.35, p = .062).

**Hemisphere, cortical gray, deep gray, and white matter level:** Examining one level down, there were no significant group effects.

**Regional level:** As there was a trend at the whole brain level, we thought to investigate regional differences. We both examined the effect of group in the full longitudinal model with all timepoints for all subjects and confirmed significant results in a simplified model that looked at group differences at baseline. Group effects were found in the right superior parietal cortical...
volume (β = -1759, p < .001) and right superior parietal white matter volume (β = -1199, p < .001) both showing reduced volume in football compared to volleyball athletes. The right hippocampus (β = -296.63, p = .001) had reduced volume, but the left pallidum (β = 142.31, p = .004) had increased volume in football compared to volleyball athletes. Interestingly, contralateral effects both showed similar trends but did not pass FDR correction: reduced left hippocampal volume (p = .009), larger right pallidum (p = .015, Figure 2). All results remained statistically significant after removal of two outliers (one in the right hippocampus in football, and the other in the left pallidum in volleyball).

Figure 2. Group differences in volume. Top) On average, football athletes show lower volume in the right superior parietal gray and white matter. Middle) Left and right hippocampal volumes are decreased in football athletes. Bottom) The left and right pallidum volumes are greater in football. All results pass FDR correction except for those labeled with #, which are p < .02.
uncorrected. Plotted values are at baseline, and statistics are adjusted for total intracranial volume and all effects remain statistically significant after the removal of outliers (solid black dots).

### 3.3. Effect of time: Age-related cortical volume loss and thinning over time

**Whole brain level:** Across all players (irrespective of sport), total brain volume decreased over time ($\beta = -7172$ mm$^3$/year, $p < .001$).

**Hemisphere, cortical gray, deep gray, and white matter level:** Interrogating down to total brain volume components, cortical gray matter volume and both left and right cortical thickness decrease over time as expected in this age range (total gray matter volume decrease: $\beta = -7849.98$ mm$^3$/year, $p < .001$), left hemisphere cortical thickness decrease: $\beta = -.022$ mm/year, $p < .001$), right hemisphere cortical thickness decrease: $\beta = -.021$ mm/year, $p < .001$). Whole-brain deep gray matter also decreased in volume over time ($\beta = -250.38$ mm$^3$/year, $p < .001$) and whole-brain white matter showed a moderate increase in volume with time ($\beta = 1098.54$ mm$^3$/year, $p = .031$).

**Regional level:** All regions with a significant group by time interaction also had a main effect of time, indicating that in these regions, across groups, volume and thickness decrease with time (see Table 3).

### 3.4. The interaction of sport and time: Differences in volume trajectory and thinning between sports

**Whole brain level:** There was a differential sport-related trajectory (i.e., a group by time interaction) in total brain volume ($\beta = 2778$ mm$^3$/year between sports, $p = .019$), with less steep thinning in football compared to volleyball.

**Hemisphere, cortical gray, deep gray, and white matter level:** Examining the source of this change, left hemisphere cortical thickness ($\beta = .01$ mm/year between sports, $p = .041$) and total cortical gray matter volume ($\beta = -2276.21$ mm$^3$/year between sports, $p = .028$) had significant group by time interactions. In all cases, less age-related decrease over time in volume and thickness were present in football compared to volleyball athletes (Figure 3, Table 2). This differential change between sports in left hemisphere cortical thickness was .34%/year, and in total cortical gray matter volume was .42%/year. No significant interaction was found in total white matter or deep gray matter volume.

**Regional level:** For both cortical thickness and cortical volume, group by time interactions were observed in the left lateral orbital frontal, left superior temporal, and left postcentral regions (Figure 4, Table 3). Again, cortical thinning and volume loss were less over time in football compared to volleyball. Cortical thickness, but not volume, showed additional effects in the left temporal pole and left cuneus (Table 3).

The inclusion or exclusion of volleyball athletes who suffered an in-study concussion had no material effect. After the re-inclusion of their post-concussion timepoints (which were originally
excluded), or exclusion of all timepoints from the control subjects who experienced an in-study concussion, the interaction between sport and time remained for both total brain volume (p = .019 re-inclusion, p=.019 full exclusion), left hemisphere cortical thickness (p = .033, p = .042), and total cortical gray matter volume (p = .027, p = .037).

To ensure we were not missing potential effects canceling each other out in the composite deep gray and white matter, we did a post-hoc regional analysis separately within the deep gray and white matter regions but did not find any regions surviving FDR correction.

Figure 3. Football athletes show less developmental thinning and volume reduction with time. This effect is seen in total cortical volume and left hemisphere cortical thickness (i.e. group by time interaction). Scatter plots are adjusted for eTIV and age at baseline MRI. Lines connect individual subjects across multiple scans.
Figure 4. Regions with divergent age-related trajectories in football athletes. In volleyball athletes, cortical thickness and cortical gray matter volume show age-related decreases (blue). A-C) Highlighted regions with divergent trajectories where football athletes show less age-related decrease in volume and thickness. A) Regions with divergent thickness over time, B-C) regions with divergent thickness and volume over time.

3.5. Within-football analyses

3.5.1. The effects of prior years of tackle football

Volumes: Total or cortical gray, deep gray, or white matter brain volume did not have a statistically significant association to years of playing football, either at baseline or as an interaction affecting these measures over time.

Thickness: The years of prior football had a positive relationship with cortical thickness at the time of the baseline MRI (left hemisphere: $\beta = .010$, $p = .012$, right hemisphere: $\beta = .011$, $p = .005$, see Figure 5). No interaction was found between prior years of football and time on cortical thickness. We verified this by regressing cortical thickness at the time of baseline MRI with the number of years playing football (i.e. without any longitudinal data), and confirmed the same positive relationship between priors years of football and left and right hemisphere thickness (left hemisphere: $\beta = .011$, $p = .013$, right hemisphere: $\beta = .012$, $p = .005$).
Figure 5. Within the football group, the number of years playing tackle football relates to greater left and right hemisphere cortical gray matter thickness (baseline thickness is depicted).

3.5.2. The effects of concussion

In order to examine the effect of prior and within-study concussions on cortical thickness and volume within the football group, our linear mixed effects model employed a binary variable indicating whether the subject had an either prior and/or in-study concussion (26 without, 24 with a history of concussion).

Volumes: No significant main or time-interaction effects were seen for total brain volume, cortical gray, and deep gray matter measures. No main effect was present for white matter volume. However, a significant concussion by time interaction was found for white matter volume (p=.036), indicating that players without a history of concussion show a greater increase in white matter volume than those with a history of concussion (Figure 6, right).

Thickness: There was a concussion by time interaction for both the left (β = .0106, p=.021) and right hemisphere cortical thickness (β = .0113, p=.020), indicating that players with a history of concussion show less cortical thinning compared to those without a history of concussion (Figure 6). We further delved into the specific concussion history by doing post-hoc analyses separate for prior concussion and in-study concussion for both the left and the right hemisphere thickness. This showed that prior concussion (interaction between time and prior concussion: left p = .037, right p = .0196) was the main driver of this effect as opposed to in-study concussion (interaction between time and in-study concussion: left p > 0.1, right p > 0.1). No main effect was detected for cortical thickness at the time of baseline MRI.
Figure 6. Longitudinal evolution of left and right hemisphere thickness and white matter volume in football players with vs. without a history of concussion (either during the study or before study enrollment). The decrease in cortical thickness with time and the increase in white matter volume with time is attenuated in subjects with a history of concussion.

3.5.3. The effects of player position
To answer the question of whether player position affects volume or thickness measures over time, a mixed effects model tested if volume or thickness measures were related to literature values of an impact severity metric called HITsp (Crisco et al., 2011) for the positions of players in this study. HITsp ranges from 28.9 to 36.1 (median 31) in our cohort, and these numeric values were used in our linear mixed effects model. In order to plot interactive effects (Figure 7, top), we separated HITsp into high and low categories as defined as players with HITsp above and below the median (low HITsp: n=31 athletes, high HITsp: n=19 athletes).

Volume: For deep gray matter volume, we found no main effect, but there was an interaction between HITsp and time after baseline MRI (β = -23.52, p=.002), indicating less of a decrease in deep gray matter volume for those with higher HITsp (i.e. greater position-based head impact risk, Figure 7, top). No effects were found across total, cortical, or white matter volume.

Within the deep gray, this interaction was significant in the left and right caudate (left: β = 5.99, p=.047, right: β = 8.78, p=.008) and left and right putamen (left: β = 14.85, p=.001, right: β = 8.27, p=.031).

Thickness: No effects were found for thickness measurements.

3.5.4. Correlation with baseline SCAT score
We also performed analysis to determine a relationship with the player’s SCAT scores at baseline and the baseline and longitudinal volume/thickness measures. SCAT scores ranged from 42 to 67 (median of 55), with a higher score indicating better performance. In order to plot interactive effects (Figure 7, bottom), we separated SCAT scores into high and low categories above and below the median, respectively (low SCAT: n=28 athletes, high SCAT: n=28 athletes).

Volume: For deep gray matter volume, we found no main effect, but there was an interaction between SCAT score and time after baseline MRI (β = -24.20, p=.023), indicating a greater decrease in deep gray matter volume for those with higher SCAT score (Figure 7). No effects were found across total, cortical, or white matter volume.

Within the deep gray, this interaction was significant in the right caudate (β = -4.44, p=.021).

Thickness: No effects were found for thickness measurements.
Figure 7. Players with higher literature values of position-based impact severity have an attenuated decrease in deep gray volume with time compared to players with lower literature values of position-based impact severity (interaction effect: $p = .002$). Similarly, players with lower SCAT scores (worse performance) had an attenuated decrease in deep gray matter volume with time compared to players with higher SCAT scores (interaction effect: $p = .023$).

4. Discussion

This study examined cortical thickness and volume change in football and volleyball athletes across multiple seasons of collegiate sports. In football athletes, we found less decrease in thickness and volume with age compared to a similar athletic cohort of volleyball players. This effect was present in total cortical gray matter volume and left hemisphere cortical thickness. In absolute terms, the 1.4% annual decrease in total cortical volume was instead approximately 1.0% in football. The group by time interaction at the largest level of the neocortex reflected underlying effects distributed over the cortex, with the largest peaks in temporal, parietal occipital, and orbitofrontal regions. More years of experience playing tackle football before enrollment in the study was similarly related to increased cortical thickness at the time of baseline scanning. A history of concussion before or during the study was associated with less cortical thinning over time compared to players with no history of concussion. Players in positions with greater literature-reported impacts to the head also had less thinning over time. Finally, lower SCAT scores at baseline were related to less subsequent deep gray matter volume.

The finding of increased cortical thickness at first glance may be counterintuitive, as one may expect atrophy from injury. However, in late adolescence and early adulthood, the typical trajectory of structural brain change is characterized by cortical thinning and decreases in cortical
volume with time (Giedd et al., 2009; Narvacan et al., 2017; Shaw et al., 2008; Tamnes et al., 2017; Wierenga et al., 2014). While the exact neurobiological mechanisms underlying these changes are still incompletely understood, less cortical thickness and volume decrease over time in college football athletes could potentially reflect differences in axonal caliber and myelination (Benes, Turtle, Khan, & Farol, 1994; Yakovlev & Lecours, 1967). Recent work has also suggested that increased myelin alters the contrast between gray and white matter, affecting the apparent contrast of the cortical boundary, and possibly decreasing measures of cortical thickness (Natu et al., 2019). Although speculative, our observed decreased rate of cortical thinning could partially be related to decreased myelination with age in football athletes. Alternatively, there may be reduced synaptic pruning compared to controls (Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011; Tamnes et al., 2017). Outside of deviations within these normative processes, it also remains possible that cumulative head impacts could induce subtle prolonged states of neuroinflammation, swelling, or compensatory hypertrophy (Bigler, 2018; Mckee & Daneshvar, 2015) that alter cytoarchitectural development. It is also possible exposure to head impacts may change the activation state of microglia, which may alter the degree of neuroinflammation, wound repair, debris clearance and phagocytosis (Cherry, Olschowka, & O’Banion, 2014; Koenigsknecht-Talboo & Landreth, 2005; Zhou et al., 2017). Because the longitudinal divergence between sports was most significant in the left hemisphere, there could be a component of compensatory hypertrophy. Finally, we cannot exclude other factors outside of sport, such as behavioral, genetic and developmental differences.

In a separate analyses examining relationships within football athletes, years of tackle football played before study enrollment, history of concussion, position-based impact severity, and SCAT scores (which includes a cognitive assessment), were all related to less normative cortical thinning with time. That is, more years of football, concussion history, impact severity, and lower SCAT performance were associated with greater gray matter volume/thickness. This may possibly reflect the same underlying unknown mechanism as for the longitudinal differences between football and volleyball. As opposed to gray matter, which declines through childhood and into adulthood, white matter volume progressively increases with age (Courchesne et al., 2000; Sowell et al., 2003). Although we did not find group level differences in the white matter volume trajectories between football and volleyball, we found that within football, players with a history of concussion showed an attenuated white matter increase with age compared to athletes without a history of concussion. Future work will evaluate diffusion tensor imaging to further interrogate microstructural alternations in these athletes.

Although concussive events may play an acute role in altering structural development, it is likely that these changes are also mediated by sub-concussive events. Years of football exposure, position-based impact severity, and a history of prior concussions all predispose players to more sub-concussive impacts. Further, our results suggest that prior, rather than in-study concussions were a main driver of the observed thickness changes, suggesting that cumulative impact exposure over time might play a larger role that acute effects of concussion. However, these results should be interpreted with caution due to reduced statistical power in the in-study concussion group and the different time since impact between the two groups. Therefore, we cannot ascertain with confidence whether cortical volume and thickness alterations are primarily sub-concussive or concussive in etiology, or both (Champagne, Coverdale, Germuska, Bhogal, & Cook, 2019; Davenport et al., 2014; Hirad et al., 2019; Talavage et al., 2014). Future work with a
larger set of concussion cases could better discern the timing of alterations in cortical thickness and volume.

To our knowledge, this work is the first multi-season longitudinal study examining age-related trajectories in cortical volume and thickness in athletes. Previous literature examining cortical thickness and volume change in high-impact sports have been relatively sparse and their findings have been inconsistent. For instance, there is some evidence that the cortex may increase in thickness after mTBI (Dall’Acqua et al., 2017; Wang et al., 2014; Wilde et al., 2012) and that impact exposure could alter normal developmental thinning (Albaugh et al., 2015). These studies have argued that cortical thickness increases could be interpreted as compensatory hypertrophy in response to an injury. However, other work has found both cortical thickening and thinning (Govindarajan et al., 2016) or no change brain structure after one season of football (Slobounov et al., 2017). Others report decreased cortical thickness, but only in athletes with a history of concussion (Meier et al., 2015) and in aging athletes gray matter reductions and increased ventricle size have been reported (Sebastien Tremblay et al., 2013). However, this previous work was cross-sectional or only over the course of one season, potentially missing longer-term cumulative changes. Since our data has up to 4 years of follow-up per subject, our analysis may be sensitive to slower changes over time, reinforced by utilization of FreeSurfer’s longitudinal pipeline (Reuter, Schmansky, et al., 2012) combined with our blinded quality control procedures.

Another source of variance is the age, severity, and lifetime cumulated exposure of the subjects. For instance, cortical thinning is observed in retired football athletes (Adler et al., 2018; Manley et al., 2017) and previous work suggests that atrophy may occur only years later in the course of mTBI (J. M. Ling, Klimaj, Toulouse, & Mayer, 2013). It is possible that for the majority of regions, atrophy may only occur later in adulthood or in response to more severe brain injuries, while in young adulthood there may be different mechanisms involved. The time since injury may also play a role in the direction of these effects. For example, animal studies suggest that even mild impacts can cause rapid focal thickening, followed by progressive thinning (Lewén et al., 1999). Furthermore, patients who experienced motor vehicle injuries showed an increase in regional thickness shortly after injury, which was followed by thinning several months after the event (Wang et al., 2014). Long-term research should explore whether early alterations in developmental trajectories are a precursor for atrophy later in life.

Not all brain regions responded in the same way and some areas were affected both at baseline and throughout the duration of the study. Specifically, football athletes had reduced baseline volume in the right hippocampus and the right superior parietal region, but increased baseline volume in the left pallidum. In accordance with our work, multiple groups have shown that sports-related impacts are associated with smaller hippocampal volumes (Parivash et al., 2019; Singh et al., 2014), adding to a growing body of evidence suggesting that the hippocampus may be particularly vulnerable to participation in high-impact sports. Our prior work examining hippocampal subfields found that the CA1 decreased in football compared to volleyball players over time (Parivash et al., 2019). It is likely that for mild sports-related impacts, multiple subtle mechanisms manifest differentially by brain region. Potential sports-related alterations are presumably superimposed on the background of differential changes across the brain: the hippocampus is still growing in early adulthood possibly because of dentate neurogenesis, while the cortex is still thinning related to pruning. Additionally, there may be geometric and/or
susceptibility differences in regional brain effects. Taken together, this may explain why some areas may be more vulnerable to head-impact and volume reductions across this time-window (i.e. the hippocampus) but other regions show a more complex profile affecting developmental trajectories across the collegiate years (i.e., in the frontal and temporal cortices).

There are some limitations of the present study. We used self-report of individual concussion history and cannot assess for under-reported prior concussions, though this is a limitation inherent to all studies on athletes. All subjects enrolled were males from only one institution, so our future work will span institutions and sexes. While history of participation in other high-impact sports was not assessed, we did assess for the more high-yield risk factors of prior years of tackle football and concussion history in both groups. Prior years of football was also a self-reported measure, which may be subject to misreporting. Finally, while SCAT total scores were evaluated in the current study, other well-validated tools, such as immediate post-concussion assessment and cognitive testing (ImPACT), as well as detailed SCAT sub-scores, could be used to better assess relationships between cognition and structural changes in the brain.

Concern could be raised that altered gray matter volume reduction in the football group could be of clinical significance. This is partially supported by the within-football effects (with years of football, concussion history, SCAT scores at baseline, and player position) mirroring the same effects as the football vs. volleyball comparison. However, it remains fundamentally unclear at this time if this longitudinal difference has a clinically significant long-term impact. Addressing this question should be the subject of future work.

In summary, we found baseline differences and divergent trajectories of cortical thickness and volume in athletes exposed to multiple years of collegiate football. These findings highlight the need for further investigations with longitudinal multi-site studies, as well as further research into the underlying mechanisms and clinical implications of these changes.

**Acknowledgements**

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**References**


Psychophysiology. https://doi.org/10.1016/j.ijpsycho.2017.09.005
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### Volume: Regional Level

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### Cortical Thickness: Regional Level

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<tr>
<td>Left Cuneus</td>
<td>0.8357</td>
<td>0.01(-0.05,0.07)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>