Relationship of Collegiate Football Experience and Concussion With Hippocampal Volume and Cognitive Outcomes

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**IMPORTANCE** Concussion and subconcussive impacts have been associated with short-term disrupted cognitive performance in collegiate athletes, but there are limited data on their long-term neuroanatomic and cognitive consequences.

**OBJECTIVE** To assess the relationships of concussion history and years of football experience with hippocampal volume and cognitive performance in collegiate football athletes.

**DESIGN, SETTING, AND PARTICIPANTS** Cross-sectional study conducted between June 2011 and August 2013 at a US psychiatric research institute specializing in neuroimaging among collegiate football players with a history of clinician-diagnosed concussion (n = 25), collegiate football players without a history of concussion (n = 25), and non–football-playing, age-, sex-, and education-matched healthy controls (n = 25).

**EXPOSURES** History of clinician-diagnosed concussion and years of football experience.

**MAIN OUTCOMES AND MEASURES** High-resolution anatomical magnetic resonance imaging was used to quantify brain volumes. Baseline scores on a computerized concussion-related cognitive battery were used for cognitive assessment in athletes.

**RESULTS** Players with and without a history of concussion had smaller hippocampal volumes relative to healthy control participants (with concussion: $t_{48} = 7.58; P < .001$; mean difference, 1788 μL; 95% CI, 1317-2258 μL; without concussion: $t_{48} = 4.35; P < .001$, mean difference, 1027 μL; 95% CI, 556-1498 μL). Players with a history of concussion had smaller hippocampal volumes than players without concussion ($t_{48} = 3.15; P < .001$; mean difference, 761 μL; 95% CI, 280-1242 μL). In both athlete groups, there was a statistically significant inverse relationship between left hippocampal volume and number of years of football played ($t_{46} = −3.62; P < .001$; coefficient = −43.54; 95% CI, −67.66 to −19.41). Behavioral testing demonstrated no differences between athletes with and without a concussion history on 5 cognitive measures but did show an inverse correlation between years of playing football and reaction time ($ρ_{42} = −0.43; 95% CI, −0.46 to −0.40; P = .005$).

**CONCLUSIONS AND RELEVANCE** Among a group of collegiate football athletes, there was a significant inverse relationship of concussion and years of football played with hippocampal volume. Years of football experience also correlated with slower reaction time. Further research is needed to determine the temporal relationships of these findings.
Concussions are clinically heterogeneous, with early and late symptom manifestations across multiple domains. History of concussion has been associated with prolonged disrupted cognitive performance in collegiate athletes. Similarly, the accumulation of subconcussive hits across a single high school football season inversely correlates with both behavioral and neuroimaging measures of working memory performance. To date, there are no definitive studies of the long-term neuroanatomical correlates of concussion history and length of exposure to contact sports in young collegiate athletes.

The hippocampus is a brain region involved in regulating multiple cognitive and emotional processes affected by concussion and is particularly sensitive to moderate and severe traumatic brain injury (TBI). Emerging evidence suggests that the hippocampus is also vulnerable to mild TBI, as indicated by volume reduction and postconcussion disruption of hippocampal function and connectivity. Even in the absence of concussion, compromised white matter integrity has been documented in the hippocampus of collegiate contact-sport athletes. In animal models, repetitive mild TBI injuries rapidly induce reactive gliosis and neuronal death in the hippocampus, resulting in cognitive impairment and memory deficits. Similarly, neurochemical markers of glial cell proliferation in the medial temporal lobe has been reported in retired athletes with a history of concussions. Combined, these findings add to the evidence that the hippocampus is highly sensitive to concussive events. However, the neuroanatomical effects of concussion on the hippocampus in young athletes with a history of concussion are not well defined.

This cross-sectional study investigates relationships among years of football playing experience and history of concussion with cognitive performance and hippocampal volume in collegiate football players. We hypothesized that concussion history would be inversely correlated with hippocampal volume and cognitive performance.

Methods

Participants
Consecutive cases of healthy National Collegiate Athletic Association Football Bowl Subdivision Division I football athletes with (n = 25) or without (n = 25) a history of clinician-diagnosed concussion and age-, sex-, and education-matched non-athlete healthy controls (n = 25) with no history of brain trauma participated in this study between June 2011 and August 2013 (for field positions see eTable 1 in the Supplement). All participants provided written informed consent approved by a local institutional review board and reported no history of alcohol or substance abuse or diagnosis of neurological or psychiatric disorders (eAppendix in the Supplement).

MRI Acquisition and Volumetrics
Magnetic resonance imaging (MRI) was performed using a GE Discover MR750 3-Tesla whole-body MRI scanner (General Electric Healthcare) and brain-optimized 32-channel arrayed head coil (Nova Medical Inc). T1-weighted anatomical images were collected using a parallelized magnetization-prepared rapid gradient-echo sequence (see the eAppendix in the Supplement for imaging details). Quantitative measurement of the hippocampus and supratentorial brain volumes was performed using FreeSurfer version 5.1. Visual inspection of the FreeSurfer-based segmentations was performed to confirm appropriate spatial registration, proper skull stripping, and accurate identification of the hippocampus in all participants. To account for inaccuracies in the FreeSurfer volumes, all FreeSurfer-generated hippocampal borders were manually inspected and edited by trained researchers blinded to group assignment following anatomical markers outlined by Franko et al.

Assessment

Years of organized tackle football played at any competitive level were self-reported. Inclusion in the athletes with concussion group involved at least 1 incidence of a clinician-diagnosed concussion with imaging occurring at least 1 month after the first concussion.

In athletes only, cognitive testing prior to start of their first football season on campus was performed using the Immediate Post-Concussion Assessment and Cognitive Testing battery (ImpACT, version 2.0 and 2.1, ImpACT Applications Inc) at the university facilities by athletic training staff who were not blinded to players’ concussion history. The percentile scores for 3 composite measures (verbal memory, visual memory, and reaction time) and the raw impulsivity score were used for analyses. The composite measures are expressed in percentile scores that can range from 0%, indicating worst possible performance, to 100%, indicating best possible performance. Raw impulsivity scores can range from 0, indicating best performance, to 20, indicating worst performance measurable from valid tests.

Statistical Analysis

Sample size was calculated to detect a standardized effect size of 1.39 in hippocampal volume differences associated with mild TBI, based on findings from a childhood TBI study. Power analysis resulted in a minimum of 21 participants per group for a power of 80% at α < .001 for a 2-sided test. Interrater reliability in hippocampal volumes between border editors was calculated using the Cronbach α. A mixed-design analysis of covariance was performed using hemisphere as a within-group factor, group membership as a between-group factor, and age and supratentorial brain volume as covariates to analyze hippocampal volumes. Planned contrasts were conducted to investigate differences in mean hippocampal volume for all combinations of groups. Effect sizes (Cohen d) were computed to demonstrate the magnitude of observed differences. For athletes, 2 linear regression analyses were performed to investigate the relationship between hippocampal volume and 4 composite baseline cognitive testing scores, and to investigate the relationship of number of prior concussions and years of football experience on hippocampal volume. Supratentorial
volume and age were covariates for all linear regression analyses. Spearman rank correlations were used to determine the relationship among years of football played and number of prior concussions with baseline composite cognitive testing scores. Correlations were corrected to a 2-sided family-wise error rate of .05 using Bonferroni correction for 8 correlations ($P < .00625$). Pairwise deletion was used to account for missing data. Statistical analyses were conducted using Systat software, version 13. The means, mean differences, and 95% confidence intervals for each comparison are presented in the Table.

## Results

Demographic reliability for the morphometric edits of 11 randomly selected FreeSurfer volumes (controls = 5; athletes without history of concussion = 3; athletes with a history of concussion = 3) was high for left hippocampus ($r = 0.97$; 95% CI, 0.92-0.99) and right hippocampus ($r = 0.98$; 95% CI, 0.94-0.99). The time between participants’ most recent clinician-diagnosed concussion and MRI data collection averaged 270 days (95% CI, 91-453 days; range, 1-1672 days).

Analysis of hippocampal volume, shown in Figure 1, revealed a significant main effect for group ($F_{2,70} = 29.06; P < .001$) (Table) but no main effect for hemisphere ($F_{1,70} = 1.24; P = .27$; mean difference, 67.59; 95% CI, 23.21-111.96) or group by hemisphere interaction ($F_{2,70} < 1.0$). In the left hemisphere, hippocampal volume was 14.1% smaller for athletes with no history of concussion and 23.8% smaller for athletes with a history of concussion relative to controls. Planned comparisons demonstrated significant differences in left hippocampal volume (Figure 1A) across all combinations of groups. (For controls vs athletes with a history of concussion, $t_{48} = 7.32; P < .001; d = 2.11$. For controls vs athletes with no history of concussion, $t_{48} = 4.17; P < .001; d = 1.20$. For athletes with no history of concussion vs athletes with a history of concussion, $t_{48} = 3.08; P = .003; d = 0.89$.)

Similarly, right hippocampal volume was 16.7% smaller for athletes with no history of concussion and 25.6% smaller for athletes with a history of concussion relative to controls. Planned comparisons in the right hemisphere hippocampal volume showed significant differences among all combinations of groups. (For controls vs athletes with a history of concussion, $t_{48} = 7.48; P < .001; d = 2.15$. For controls vs athletes with no history of concussion, $t_{48} = 4.29; P < .001; d = 1.23$. For athletes with no history of concussion vs athletes with a history of concussion, $t_{48} = 3.11; P = .003; d = 0.90$.) For comparison, unedited hippocampal and amygdala volumes were analyzed (eAppendix, eTable 2, eFigure 2, and eFigure 3 in the Supplement).

Baseline cognitive testing was unavailable for 4 athletes, as was the number of years played for 2 athletes. Regression analyses revealed that left hippocampal volume was significantly inversely related to years played ($t_{46} = -3.62; P < .001; d = -1.08$; coefficient = $-43.54$; 95% CI, $-67.66$ to $-19.41$) but not to number of prior concussions ($t_{45} = -1.40; P = .17; d = 0.44$; coefficient = $-61.80$; 95% CI, $-150.49$ to 26.89). Right hippocampal volume was not significantly related to either years played ($t_{45} = -1.03; P = .31; d = -0.30$; coefficient = $-21.93$; 95% CI, $-64.85$ to $-20.98$) or number of prior concussions ($t_{45} = -1.46; P = .15; d = -0.44$; coefficient = $-119.60$; 95% CI, $-218.60$ to $-2.68$).

Additional linear regression models found no significant relationship between right hippocampal volume (full model, $F_{6,39} = 1.24; P = .31$) or left hippocampal volume (full model, $F_{6,39} = 1.12; P = .37$) and cognitive testing measures (for regression coefficients and 95% confidence intervals see eTable 3 in the Supplement). Cognitive testing measures did not differ between athletes with and without a concussion history. However, Spearman correlations showed an inverse relationship between baseline reaction time percentile score and number of years played ($r_{42} = -0.43$; 95% CI, $-0.46$ to $-0.40$; $P = .005$; Pearson $r = -0.48$; 95% CI, $-0.50$ to $-0.45$; $P = .005$) (Figure 2).

## Discussion

The present study reports smaller bilateral hippocampal volumes in collegiate football athletes compared with healthy control participants. This correlation was larger in participants with a history of concussion. Number of years of football-playing experience was inversely associated with both left hemisphere hippocampal volume and baseline reaction time. These results extend existing literature showing slowed reaction time associated with history of concussion by demonstrating slowed reaction times related to exposure to tackle football regardless of concussion history.

The interpretation of hippocampal volumetric differences is complicated by multiple factors including genetics, environment, hormones, growth factors, and neurodevelopmental trajectory. Among the most consistent findings associated with smaller hippocampal volumes are high levels of stress-related hormones. Collegiate athletes have been exposed to both physical and psychological stressors throughout their careers. These stressors could produce an excess of glucocorticoid secretion that may act to suppress neurogenesis and decrease dendritic arborization within the hippocampus. This effect is likely mediated by genetics, and although a large multinational consortium recently identified a single-nucleotide polymorphism associated with hippocampal volume and poorer verbal memory, assessing the role of genetics in concussion was slowed by the requirements of very large sample sizes. The present study design limits our ability to dissociate among the many possible factors involved in these hippocampal volume findings, but our study should serve as an impetus for future longitudinal research to investigate the neuroanatomical and cognitive changes in young contact-sport athletes. The clinical significance of the observed hippocampal size differences is unknown at this time.

Limitations of this study warrant discussion. First, the cross-sectional design prevents inferences regarding causality and temporality about the relationship between years of
Table. Demographics, Cognitive Test Scores, and Brain Volumetrics of Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD) [95% CI]</th>
<th>F Statistic or t Statistic</th>
<th>Mean Difference (95% CI)</th>
<th>P Valuea</th>
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</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>20.8 (1.87)</td>
<td>[20.03-21.57]</td>
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<tr>
<td>Education, y</td>
<td>13.26 (1.44)</td>
<td>[12.77-13.95]</td>
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<tr>
<td>Football experience, y</td>
<td>0</td>
<td>[9.37-11.63]</td>
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<tr>
<td><strong>Diagnosed concussions, No. of participants</strong></td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>1-2</td>
<td>15</td>
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<tr>
<td>3-5</td>
<td>10</td>
<td></td>
<td></td>
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<tr>
<td>Days since last diagnosed concussionb</td>
<td>270.8 (439.7)</td>
<td>[89.4-452.3]</td>
<td></td>
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<tr>
<td><strong>Cognitive test scoresc</strong></td>
<td></td>
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<tr>
<td>Reaction time, %</td>
<td>67.83 (26.84)</td>
<td>[56.22-79.43]</td>
<td></td>
<td></td>
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<tr>
<td>Verbal memory, %</td>
<td>57.04 (29.07)</td>
<td>[44.47-69.61]</td>
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<tr>
<td>Visual memory, %</td>
<td>53.00 (36.11)</td>
<td>[37.38-68.62]</td>
<td></td>
<td></td>
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<tr>
<td>Motor speed, %</td>
<td>56.00 (23.41)</td>
<td>[45.88-66.12]</td>
<td></td>
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<tr>
<td>Impulse control</td>
<td>6.87 (4.52)</td>
<td>[4.92-8.82]</td>
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<tr>
<td><strong>Brain region volume, μL</strong></td>
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<tr>
<td>Supratentorial</td>
<td>1 169 000 (136 145)</td>
<td>[1 113 000-1 225 000]</td>
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<tr>
<td>Total hippocampus</td>
<td>7572 (1084)</td>
<td>[7124-8019]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>3746 (541)</td>
<td>[3532-3970]</td>
<td></td>
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<tr>
<td>Right hippocampus</td>
<td>3926 (556.6)</td>
<td>[3596-4055]</td>
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<tr>
<td><strong>Brain volume ratio</strong></td>
<td></td>
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<tr>
<td>Controls vs athletes without history of concussion</td>
<td>3.35 (1.42)</td>
<td>[2.16-4.52]</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Controls vs athletes with history of concussion</td>
<td>3.95 (1.23)</td>
<td>[2.72-5.18]</td>
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<td>&lt;.001</td>
</tr>
<tr>
<td>Athletes without vs with history of concussion</td>
<td>3.48 (1.57)</td>
<td>[2.35-4.62]</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Controls vs athletes without history of concussion</td>
<td>4.17 (1.07)</td>
<td>[2.98-5.35]</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Controls vs athletes with history of concussion</td>
<td>4.72 (1.29)</td>
<td>[3.51-5.93]</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Athletes without vs with history of concussion</td>
<td>4.32 (1.33)</td>
<td>[3.11-5.53]</td>
<td></td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* P < .05 was considered statistically significant.

** Analysis of-variance F statistics for overall differences among groups.

† Football experience was available for 24 participants in each group.

‡ Unpaired t statistics for difference between groups.

Range, 1-1672 days.

Cognitive scores were available for 23 participants in each group.

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football experience and hippocampus volume. Unlike prior studies of sports-related concussion,2-4 and despite differences in hippocampal volume, the athlete groups showed no significant differences in baseline cognitive performance, possibly because of the relatively small sample size in the present study. Second, athletes often underreport concussion symptoms,29 which could potentially contaminate our distinction between athletes with and without a history of conc-

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*P < .05 was considered statistically significant.

‡ Football experience was available for 24 participants in each group.
discussion. Third, though evidence-based diagnostic guidelines have been outlined, differences in clinical practice could result in different thresholds for diagnosis, also affecting this study’s group classifications. Despite these limitations, the present results demonstrate that medically confirmed concussion history correlates with smaller hippocampal volume and that these smaller volumes inversely correlate with exposure to football.

Conclusions

Within a group of collegiate football athletes, there was an inverse relationship between football experience and concussion with hippocampal volume. Football experience was also correlated with slower reaction time. Further longitudinal research is needed to establish the temporal relationships of these findings.
Research Preliminary Communication

ARTICLE INFORMATION

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Author Contributions: Drs Bellgowan and Singh had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Singh, Meier, Savitz, Cavanagh, Allen, Teague, Polanski, Bellgowan. Acquisition, analysis, or interpretation of data: Singh, Meier, Kuplicki, Mukai, Nerio, Bellgowan. Drafting of the manuscript: Singh, Meier, Bellgowan. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Singh, Meier, Bellgowan. Administrative, technical, or material support: Singh, Mukai, Allen, Teague, Bellgowan. Study supervision: Singh, Polanski, Bellgowan.

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REFERENCES