Preliminary Communication

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 ($\rho_{42} = -0.43$; 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.

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Concussions are clinically heterogeneous, with early and late symptom manifestations across multiple domains.[1] History of concussion has been associated with prolonged disrupted cognitive performance in collegiate athletes.[2-4] 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.[5,6] 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).[7-10] Emerging evidence suggests that the hippocampus is also vulnerable to mild TBI, as indicated by volume reduction[11] and postconcussion disruption of hippocampal function[12] and connectivity.[13] Even in the absence of concussion, compromised white matter integrity has been documented in the hippocampus of collegiate contact-sport athletes.[14] In animal models, repetitive mild TBI injuries rapidly induce reactive gliosis and neuronal death in the hippocampus,[15] resulting in cognitive impairment and memory deficits.[16-19] Similarly, neurochemical markers of glial cell proliferation in the medial temporal lobe has been reported in retired athletes with a history of concussions.[20] 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-football player 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.[21] 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 Frankó et al[22] (eFigure 1 in the Supplement).

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)[23] 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.[11] Power analysis resulted in a minimum of 21 participants per group for a power of 80% at $\alpha<.001$ 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

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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 details of each group are listed in the Table. Interrater 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 ($t_{45} = -1.40$; $P = .17$; $d = 0.41$; 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 ($\rho_{42} = -0.43$; 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[4] 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.[24] 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.[24-26] This effect is likely mediated by genetics, and although a large multinational consortium recently identified a single-nucleotide polymorphism associated with hippocampal volume[27] and poorer verbal memory,[28] assessing the role of genetics in concussion will be 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

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Table. Demographics, Cognitive Test Scores, and Brain Volumetrics of Participants

Characteristics	Mean (SD) [95% CI] Healthy Controls (n = 25)	Athletes Without History of Concussion (n = 25)	Athletes With History of Concussion (n = 25)	*F* Statistic or *t* Statistic	Mean Difference (95% CI)	*P* Value[a]
Demographics						
Age, y	20.8 (1.87) [20.03-21.57]	20.28 (1.43) [19.69-20.87]	21.16 (1.31) [20.62-21.7]	$F_{2,72} = 2.02$[b]		.14
Education, y	13.26 (1.44) [12.77-13.95]	13.08 (1.32) [12.53-13.63]	13.44 (1.04) [13.01-13.87]	$F_{2,72} = 0.55$[b]		.58
Football experience, y[c]	0	10.50 (2.69) [9.37-11.63]	13.08 (2.48) [12.03-14.13]	$t_{46} = 3.55$[d]	−2.58 (−4.09 to −1.08)	<.001
Diagnosed concussions, No. of participants	0	0				
1-2			15			
3-5			10			
Days since last diagnosed concussion[e]			270.8 (439.7) [89.4-452.3]			
Cognitive test scores[f]						
Reaction time, %		67.83 (26.84) [56.22-79.43]	59.74 (25.82) [48.58-70.90]	$t_{44} = 1.04$[d]	8.08 (−7.58 to 23.75)	.30
Verbal memory, %		57.04 (29.07) [44.47-69.61]	59.65 (28.65) [47.26-72.04]	$t_{44} = 0.31$[d]	−2.61 (−19.77 to 14.56)	.76
Visual memory, %		53.00 (36.11) [37.38-68.62]	50.87 (35.01) [35.73-66.01]	$t_{44} = 0.20$[d]	2.13 (−19.02 to 23.28)	.84
Motor speed, %		56.00 (23.41) [45.88-66.12]	54.22 (23.45) [44.08-64.36]	$t_{44} = 0.26$[d]	1.78 (−12.15 to 15.72)	.80
Impulse control		6.87 (4.52) [4.92-8.82]	6.09 (4.75) [4.03-8.140]	$t_{44} = 0.57$[d]	0.78 (−1.97 to 3.54)	.57
Brain region volume, μL						
Supratentorial	1 169 000 (136 145) [1 113 000-1 225 000]	1 167 000 (90 053) [1 130 000-1 204 000]	1 151 000 (71 051) [1 122 000-1 180 000]	$F_{2,72} = 0.23$[b]		.80
Total hippocampus	7572 (1084) [7124-8019]	6489 (815.4) [6152-6825]	5784 (609.3) [5532-6035]	$F_{2,70} = 29.06$[g]		<.001
Controls vs athletes without history of concussion				$t_{48} = 4.35$[h]	1026.79 (555.56 to 1498.02)	<.001
Controls vs athletes with history of concussion				$t_{48} = 7.58$[h]	1787.75 (1317.32 to 2258.18)	<.001
Athletes without vs with history of concussion				$t_{48} = 3.15$[h]	760.96 (279.87 to 1242.06)	<.001
Left hippocampus	3746 (541) [3532-3970]	3219 (414.6) [3048-3390]	2855 (325.4) [2721-2990]	$F_{2,70} = 27.13$[g]		<.001
Controls vs athletes without history of concussion				$t_{48} = 4.17$[h]	505.01 (218.69 to 791.34)	<.001
Controls vs athletes with history of concussion				$t_{48} = 7.32$[h]	895.08 (608.75 to 1181.40)	<.001
Athletes without vs with history of concussion				$t_{48} = 3.08$[h]	390.10 (103.74 to 676.39)	.003
Right hippocampus	3926 (556.6) [3596-4055]	3270 (428.5) [3093-3447]	2920 (318.6) [2789-3051]	$F_{2,70} = 28.31$[g]		<.001
Controls vs athletes without history of concussion				$t_{48} = 4.29$[h]	521.90 (233.29 to 810.51)	<.001
Controls vs athletes with history of concussion				$t_{48} = 7.48$[h]	908.81 (620.20 to 1197.42)	<.001
Athletes without vs with history of concussion				$t_{48} = 3.11$[h]	386.92 (98.31 to 675.53)	<.001

[a] *P*<.05 was considered statistically significant.

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

[c] Football experience was available for 24 participants in each group.

[d] Unpaired *t* statistics for difference between groups.

[e] Range, 1-1672 days.

[f] Cognitive scores were available for 23 participants in each group.

[g] Analysis-of-covariance *F* statistics for overall differences among groups using age and supratentorial brain volume as covariates.

[h] Planned comparison across all groups for total, left, and right hippocampal volume.

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 con-

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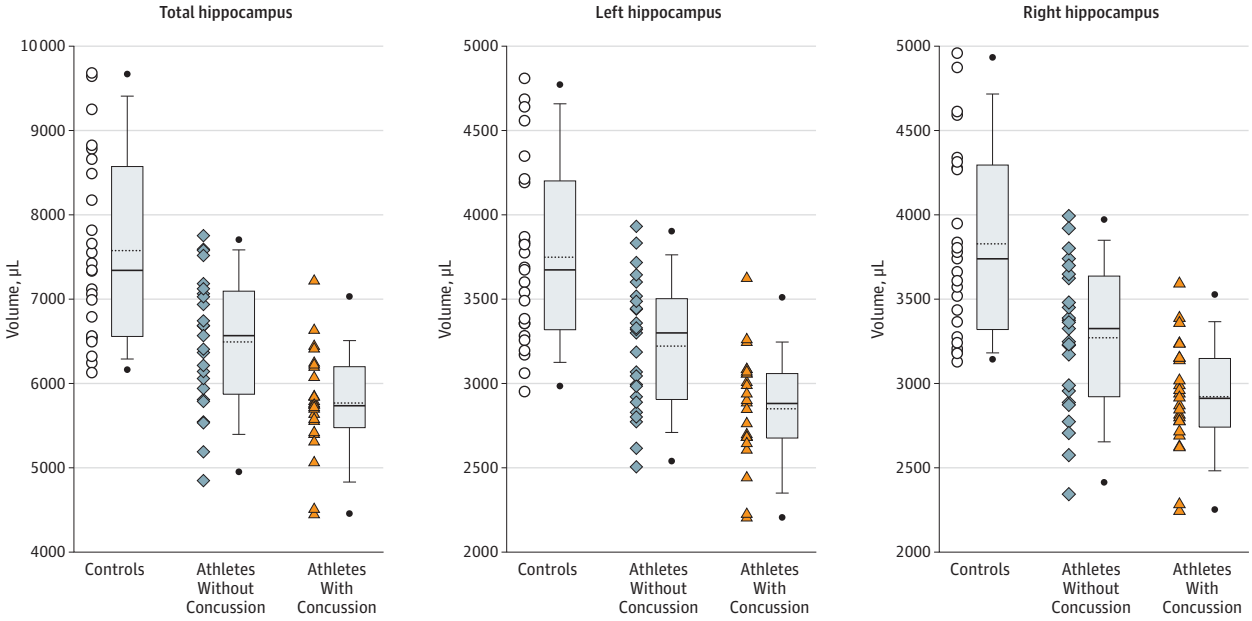
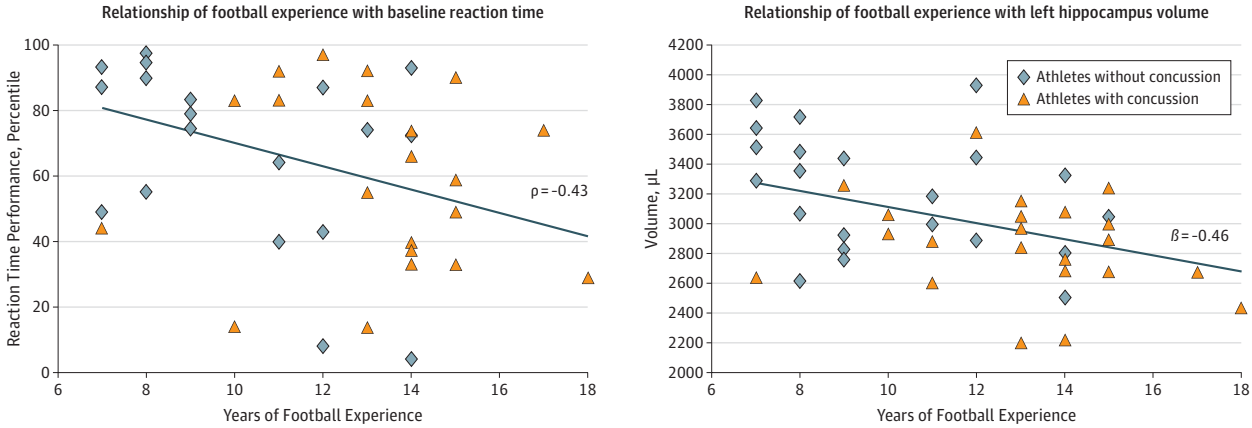
Figure 1. Smaller Hippocampal Volumes in Collegiate Football Athletes Relative to Healthy Controls



Total, left hemisphere, and right hemisphere hippocampal volumes for healthy controls (n=25), athletes with no history of concussion (n=25), and athletes with a history of concussion (n=25). Shown in each box plot are the 5th and 95th percentiles (black dots), 10th and 90th percentiles (whiskers), and 25th and 75th percentiles (box top and bottom). The median (solid line) and mean (dotted line) are also shown within each group's box. Individual volumes for each group are indicated by the symbols to the left of each group's box plot.

Figure 2. Years of Football Experience Inversely Correlate With Baseline Reaction Time and Left Hemisphere Hippocampal Volume



Left, total number of years that athletes reported having played football (x-axis) in relation to the Immediate Post-Concussion Assessment and Cognitive Testing composite reaction time score. Forty-four collegiate football players contributed data (n=22 athletes without and n=22 athletes with concussion); the regression line (blue diagonal line) is calculated for all points regardless of concussion history.

Right, relationship between years played and left hemisphere hippocampal volume. Forty-eight athletes contributed data for this plot (n=24 athletes without and n=24 athletes with concussion); the regression line (blue diagonal line) is calculated for all points regardless of concussion history. In both graphs, some data markers overlap.

cussion. Third, though evidence-based diagnostic guidelines have been outlined,[30] 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.

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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

1. Nelson LD, Janecek JK, McCrea MA. Acute clinical recovery from sport-related concussion. *Neuropsychol Rev*. 2013;23(4):285-299.

2. Collins MW, Grindel SH, Lovell MR, et al. Relationship between concussion and neuropsychological performance in college football players. *JAMA*. 1999;282(10):964-970.

3. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA*. 2003;290(19):2556-2563.

4. Covassin T, Moran R, Wilhelm K. Concussion symptoms and neurocognitive performance of high school and college athletes who incur multiple concussions. *Am J Sports Med*. 2013;41(12):2885-2889.

5. Talavage TM, Nauman EA, Breedlove EL, et al. Functionally-detected cognitive impairment in high school football players without clinically-diagnosed concussion. *J Neurotrauma*. 2014;31(4):327-338.

6. Breedlove EL, Robinson M, Talavage TM, et al. Biomechanical correlates of symptomatic and asymptomatic neurophysiological impairment in high school football. *J Biomech*. 2012;45(7):1265-1272.

7. Bigler ED, Anderson CV, Blatter DD. Temporal lobe morphology in normal aging and traumatic brain injury. *AJNR Am J Neuroradiol*. 2002;23(2):255-266.

8. Wilde EA, Bigler ED, Hunter JV, et al. Hippocampus, amygdala, and basal ganglia morphometrics in children after moderate-to-severe traumatic brain injury. *Dev Med Child Neurol*. 2007;49(4):294-299.

9. Lowenstein DH, Thomas MJ, Smith DH, McIntosh TK. Selective vulnerability of dentate hilar neurons following traumatic brain injury: a potential mechanistic link between head trauma and disorders of the hippocampus. *J Neurosci*. 1992;12(12):4846-4853.

10. Grady MS, Charleston JS, Maris D, Witgen BM, Lifshitz J. Neuronal and glial cell number in the hippocampus after experimental traumatic brain injury: analysis by stereological estimation. *J Neurotrauma*. 2003;20(10):929-941.

11. Beauchamp MH, Ditchfield M, Maller JJ, et al. Hippocampus, amygdala and global brain changes 10 years after childhood traumatic brain injury. *Int J Dev Neurosci*. 2011;29(2):137-143.

12. Slobounov SM, Zhang K, Pennell D, Ray W, Johnson B, Sebastianelli W. Functional abnormalities in normally appearing athletes following mild traumatic brain injury: a functional MRI study. *Exp Brain Res*. 2010;202(2):341-354.

13. Slobounov SM, Gay M, Zhang K, et al. Alteration of brain functional network at rest and in response to YMCA physical stress test in concussed athletes: RsFMRI study. *Neuroimage*. 2011;55(4):1716-1727.

14. McAllister TW, Ford JC, Flashman LA, et al. Effect of head impacts on diffusivity measures in a cohort of collegiate contact sport athletes. *Neurology*. 2014;82(1):63-69.

15. Hicks RR, Smith DH, Lowenstein DH, Saint Marie R, McIntosh TK. Mild experimental brain injury in the rat induces cognitive deficits associated with regional neuronal loss in the hippocampus. *J Neurotrauma*. 1993;10(4):405-414.

16. Creed JA, DiLeonardi AM, Fox DP, Tessler AR, Raghupathi R. Concussive brain trauma in the mouse results in acute cognitive deficits and sustained impairment of axonal function. *J Neurotrauma*. 2011;28(4):547-563.

17. Nakajima Y, Horiuchi Y, Kamata H, Yukawa M, Kuwabara M, Tsubokawa T. Distinct time courses of secondary brain damage in the hippocampus following brain concussion and contusion in rats. *Tohoku J Exp Med*. 2010;221(3):229-235.

18. Mouzon B, Chaytow H, Crynen G, et al. Repetitive mild traumatic brain injury in a mouse model produces learning and memory deficits accompanied by histological changes. *J Neurotrauma*. 2012;29(18):2761-2773.

19. Milman A, Rosenberg A, Weizman R, Pick CG. Mild traumatic brain injury induces persistent cognitive deficits and behavioral disturbances in mice. *J Neurotrauma*. 2005;22(9):1003-1010.

20. Tremblay S, De Beaumont L, Henry LC, et al. Sports concussions and aging: a neuroimaging investigation. *Cereb Cortex*. 2013;23(5):1159-1166.

21. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002;33(3):341-355.

22. Frankó E, Insausti AM, Artacho-Pérula E, Insausti R, Chavoix C. Identification of the human medial temporal lobe regions on magnetic resonance images. *Hum Brain Mapp*. 2014;35(1):248-256.

23. Schatz P, Pardini JE, Lovell MR, Collins MW, Podell K. Sensitivity and specificity of the ImPACT test battery for concussion in athletes. *Arch Clin Neuropsychol*. 2006;21(1):91-99.

24. McEwen BS. Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. *Ann N Y Acad Sci*. 2001;933:265-277.

25. Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. *Biol Psychiatry*. 2000;48(8):755-765.

26. Mastorakos G, Pavlatou M. Exercise as a stress model and the interplay between the hypothalamus-pituitary-adrenal and the hypothalamus-pituitary-thyroid axes. *Horm Metab Res*. 2005;37(9):577-584.

27. Stein JL, Medland SE, Vasquez AA, et al; Alzheimer's Disease Neuroimaging Initiative; EPIGEN Consortium; IMAGEN Consortium; Saguenay Youth Study Group; Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium; Enhancing Neuro Imaging Genetics through Meta-Analysis Consortium. Identification of common variants associated with human hippocampal and intracranial volumes. *Nat Genet*. 2012;44(5):552-561.

28. Erk S, Meyer-Lindenberg A, Schmierer P, et al. Functional impact of a recently identified quantitative trait locus for hippocampal volume with genome-wide support. *Transl Psychiatry*. 2013;3:e287.

29. McCrea M, Hammeke T, Olsen G, Leo P, Guskiewicz K. Unreported concussion in high school football players: implications for prevention. *Clin J Sport Med*. 2004;14(1):13-17.

30. Giza CC, Kutcher JS, Ashwal S, et al. Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013;80(24):2250-2257.

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