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Prospective study of the association between sport-related concussion and brain morphometry (3T-MRI) in collegiate athletes: A study from the NCAA-DOD CARE Consortium

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Abstract

Objectives: To determine the acute and early long-term associations of sport-related concussion and subcortical and cortical structures in collegiate contact sport athletes.

Methods: Athletes with a recent sport-related concussion (N=99) and matched contact (N=91) and non-contact sport controls (N=95) completed up to four neuroimaging sessions from 24–48 hours to 6 months post-injury. Subcortical volumes (amygdala, hippocampus, thalamus, dorsal striatum) and vertex-wise measurements of cortical thickness/volume were computed using FreeSurfer. Linear mixed-effects models examined the acute and longitudinal associations between

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concussion and structural metrics, controlling for intracranial volume (or mean thickness) and demographic variables (including prior concussions and sport exposure).

Results: There were significant group-dependent changes in amygdala volumes across visits (p=0.041); this effect was driven by a trend for increased amygdalae volume at 6-months relative to sub-acute visits in contact controls, with no differences in athletes with sport-related concussion. No differences were observed in any cortical metric (i.e., thickness or volume) for primary or secondary analyses.

Conclusion: A single sport-related concussion had minimal associations with gray matter structure across a 6-month time frame.

Introduction

The potential effects of sport-related concussion on brain structure and function have significant public health implications [1]. Sport-related concussion may be associated with several adverse outcomes later in life, such as elevated risk of neurodegenerative or psychiatric disease [2–6]. Whether there are acute or early long-term effects of a single sport-related concussion on brain morphometry has not been clearly established. Studies of former professional athletes have suggested that sport-related concussion history and contact sport exposure are associated with volume loss or cortical thinning in fronto-temporal cortex and several limbic structures [7–10], with similar reports in active collegiate athletes [11–14]. Recent studies failed to observe concussion-related changes in cortical thickness or subcortical volumes in children with mild traumatic brain injury (including sport-related concussion) recruited from the emergency department 6-months post-injury or in collegiate athletes across the first month post-injury [15,16]. Other studies of non-sport mild traumatic brain injury, however, suggest that a single injury may lead to cortical thinning [17–20] or atrophy of subcortical structures [21].

The goal of this study from the NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium was to investigate the acute and early long-term associations of sport-related concussion with cortical and subcortical structure in a large prospective sample of male and female collegiate athletes. We tested the hypothesis that a single sport-related concussion leads to thinner cortex (e.g., frontal and temporal cortex) and smaller subcortical volumes (e.g., thalamus, dorsal striatum, amygdala, and hippocampus) over a 6-month follow-up period, given the vulnerability of these regions to sport-related concussion reported previously [7,8,12,14,22].

Methods

Participants

This study was approved by the Medical College of Wisconsin Institutional Review Board and the Human Research Protection Office (HRPO). All participants provided written informed consent. There was no patient and public involvement in this study. The study design and methods of NCAA-DoD CARE Consortium have been previously described [23]. The current study involves athletes enrolled in the CARE Consortium Advanced Research Core (ARC), which includes four sites where neuroimaging protocols are

performed, beginning 24–28 hours post-sport-related concussion (baseline neuroimaging was not performed): University of Wisconsin-Madison (UW), University of North Carolina at Chapel Hill (UNC), University of California Los Angeles (UCLA), and Virginia Tech (VT). Contact sport athletes from football, ice hockey, lacrosse, and soccer were enrolled during the preseason.

Concussion was defined per the US Department of Defense consensus as "a change in brain function following a force to the head, which may be accompanied by temporary loss of consciousness, but is identified in awake individuals with measures of neurologic and cognitive dysfunction" [23,24]. Potential concussions were identified by qualified healthcare professionals (e.g., certified athletic trainers, physicians) and diagnosis of concussion was confirmed by team physicians in accord with the definition provided above. Concussed athletes (SRC) were assessed at 24–48 hours post-injury (Acute), after clearance to begin the return-to-play (RTP) protocol (Asymptomatic), seven days after their unrestricted RTP (Post-RTP), and 6 months post-injury (6-month). Non-injured contact sport athletes matched using an algorithm based on variables of institution, sport, sex, race/ethnicity, estimate of premorbid verbal intellectual functioning, concussion history, years of participation, status as a starter, and head impact exposure data (if available) completed similar visits and served as contact controls (CC). Non-contact sports athletes (i.e., baseball, basketball, cross-country/track, field event, and softball) matched on institution, sex, race/ethnicity, and estimate of premorbid verbal intellectual functioning served as additional controls (NCC; N=101).

We excluded athletes with a history of moderate/severe traumatic brain injury or seizure disorder, acute findings on MRI identified during a clinical overread by radiology, or poor scan quality before or after preprocessing (Figure 1). The final sample included 99 SRC, 91 CC, and 95 NCC athletes that completed at least a single visit with neuroimaging.

Clinical Battery

Demographic and health history information were collected at baseline visits during the preseason and at each follow-up assessment. Athletes self-reported the number of prior concussions and years of participation in their primary sport. The Wechsler Test of Adult Reading (WTAR) was collected at baseline and used to estimate pre-morbid intelligence. Concussion symptoms were assessed using the symptom severity scores from the Sport Concussion Assessment Tool – 3rd Edition symptom checklist (SCAT). Injury characteristics and recovery information were collected at post-injury visits.

Imaging Protocol and Processing

High resolution T1-weighted images (1 mm × 1 mm × 1 mm) were acquired on 3T MRI scanners at each site. A 3D magnetization-prepared rapid gradient-echo sequence was collected on Siemens MAGNETOM Prisma (32 channel head coil) and MAGNETOM Trio (32 or 12 channel head coils) scanners at UNC and UCLA with the following parameters: TR/TE/TI = 2300/2.98/900 ms, flip angle = 9 degrees, FOV = 256 mm, Matrix = 256 × 256, 176 slices, slice thickness 1 mm. A 3D magnetization-prepared rapid gradient-echo sequence was collected on the Siemens MAGNETOM Trio (8 channel head coil) scanner at

VT with the following parameters: TR/TE/TI = 2300/2.89/900 ms, flip angle = 9 degrees, FOV = 256 mm, Matrix = 256 × 256, 176 slices, slice thickness 1 mm. A 3D Brain Volume (BRAVO) sequence was collected on a General Electric Discovery MR750 scanner at UW with the following parameters: TR = 6.62 to 6.652, TE = 2.91 to 2.928, TI = 450 ms, flip angle = 12 degrees, FOV = 256 mm, Matrix = 256 × 256, 164 slices, slice thickness 1 mm. Previous work has demonstrated the stability of this imaging protocol across sites and platforms [25].

Anatomical images were automatically analyzed via the FreeSurfer 5.3 image processing suite [26,27]. The T1-images went through reconstruction of the cortical surface and tissue segmentation via removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray/white matter boundary, automated topology correction, and surface deformation with intensity gradients in order to accurately place the boundaries between gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The longitudinal processing stream was used to extract reliable volume and thickness estimates [28]. Raw (T1-images) and processed data (e.g., white matter/gray matter boundaries, subcortical segmentation) were manually graded (pass, questionable, fail) at multiple steps, including during the initial estimation and after application of the longitudinal processing stream. When necessary (e.g., questionable scans), scans were reviewed by an independent rater and consensus was formed to determine exclusion from study due to poor data quality (e.g., due to excessive motion). Prior work has demonstrated test-retest reliability and segmentation accuracy using the longitudinal Freesurfer pipeline [29–31]; thus, no manual edits were made to generated outputs that passed quality assessment procedures.

Vertex-wise cortical thickness (CT) and cortical volume (CV) were calculated across the cortical mantle and smoothed at a full-width half-maximum value of 10 mm. Segmented volumes of *a priori* subcortical regions-of-interest included bilateral (i.e. left and right hemisphere combined) thalamus, hippocampus, amygdala, and dorsal striatum (combined caudate and putamen) based on the vulnerability of these regions to brain injury [7,8,12,14,32].

Statistical Analyses

Analyses were conducted using the IBM SPSS v24 unless otherwise specified. One-way analyses of variance (with Welch's test when indicated), chi-square tests, or Fisher's Exact tests were used to compare demographic variables between groups. Linear mixed-effects (LME) models were fit to assess changes in morphometry across visits as a function of group, with the effects of group, visit, and the group-by-visit interaction. Additional covariates included prior concussion history (coded as 0, 1+), years of participation in primary sport, age, sex, BMI, estimated intracranial volume (for volume analyses), mean CT (for CT analyses), and a combined variable to account for potential site, scanner, and head coil differences. Participant was modeled as a random factor. For vertex-wise analyses of CT and CV, identical LME were fit using a spatiotemporal mass-univariate LME across the cortical surface using FreeSurfer 5.3 and Matlab 2018b [33,34]. A two-stage linear step-up

FDR correction was used to correct for multiple vertex-wise comparisons [35]. Diagnostic assessments were run for all models to confirm that their respective assumptions were not violated. An alpha of 0.05 was considered for significant effects. Effects of group and group-by-visit interactions were the independent variables of interest.

Results

Participant Characteristics and Primary Analyses

Group demographics, medical history, and injury information are provided in Table 1.

NCC athletes were significantly older and had significantly lower BMI than both CC (age: mean difference (standard error) [MD(SE)]=0.41(0.17), 95% Confidence Interval(CI)[0.07, 0.74], p=0.017; BMI: MD(SE)=−2.75(0.66), 95%CI[−4.05, −1.46], p<0.001) and SRC (age: MD(SE)=0.54(0.17), 95%CI[0.21, 0.86], p=0.001; BMI: MD(SE)=−3.85(0.64), 95%CI[−5.12, −2.58], p<0.001). SRC athletes were significantly more likely to have prior concussion than CC and NCC, while CC were more likely to have prior concussion than NCC (ps<0.05). SRC were also more likely to have ADHD compared to NCC (p<0.05). In addition, a higher proportion of SRC and CC athletes had unknown or unreported ethnicity relative to NCC (ps<0.05), while a higher proportion of NCC reported Non-Hispanic ethnicity relative to SRC (p<0.05). Three SRC participants reported experiencing LOC, 10 reported PTA, and 8 reported RGA associated with their concussion. The injured group had a mean symptom duration of 9.23 ± 6.04 days and a mean time to unrestricted return-to-play of 15.72 ± 11.21 days. As expected, SRC athletes had significantly elevated SCAT symptom severity scores relative to CC (MD(SE)=19.74(1.80), 95%CI[16.20, 23.27], p<0.001) and NCC (MD(SE)=20.16(1.79), 95%CI[16.64, 23.69], p<0.001) at the Acute visit.

Statistics for group effects (i.e., SRC, CC, and NCC) and group-by-visit interactions for subcortical structures are presented in Table 2.

There was a significant group-by-visit interaction on amygdalae volume (p=0.041; Figure 2). Post-hoc tests, however, showed only a non-significant overall visit effect (F=2.49, p=0.06) of larger amygdalae volumes in CC athletes at the 6-month visit relative to the Asymptomatic (MD(SE)=47.20(20.72), p=0.023) and Post-RTP visits (MD(SE)=42.33(21.04), p=0.045; Table 3). Amygdalae volumes in the SRC and NCC groups did not differ across visits. No other group or group-by-visit interactions were significant for subcortical volume, CT, or CV.

Discussion

This large-scale, prospective study investigated the acute and early long-term associations of a single sport-related concussion with gray matter structure in collegiate, contact-sport athletes relative to two groups of carefully matched controls. Analyses for sport-related concussion effects were null for subcortical volume and cortical volume and thickness. There was, however, a group-by-visit interaction on bilateral amygdalae volumes that was driven by increases in volume across 6 months in contact sport control athletes, which was absent in athletes with sport-related concussion and non-contact controls. Overall, the

current results suggest that the association between an isolated sport-related concussion and macroscopic gray matter structure is minimal during the acute and early long-term phases post-injury (i.e., 6 months).

The group-by-visit effect on the amygdalae in our study was driven by a non-significant increase in volume at the 6-month visit in contact sport controls, as opposed to post-injury changes in concussed athletes. While it is conceivable that sport-related concussion may attenuate increases in amygdalae volume that are observed in contact controls over the same time period (e.g., due to disrupting typical amygdalae development, which non-linearly increases in volume into late-adolescence [36]) it is important to note that follow-up tests did not identify a significant change in amygdalae volume across visits in any of the three groups. Thus, the observed interaction was due to non-significant changes in opposing directions between groups. Additional work is needed to replicate this finding and provide additional insight into its underlying mechanism and clinical relevance, if any. However, given the lack of strength of this finding, combined with the null findings for the other subcortical and cortical analyses and the relatively large sample size, current results largely suggest that *typical* sport-related concussion is minimally associated with gray matter structure over the course of 6 months, consistent with prior results [15,16].

There are previous reports of structural aberrations during the acute and sub-acute phases in patients with non-sport-related mild traumatic brain injury, with multi-regional volume differences observed as early as one week and as late as one year post-injury [17,19,21,37–39]. There are several potential explanations for the apparent discrepancies between non-sport samples and the current work. First, the concussions studied in this manuscript are likely on the milder spectrum of mild traumatic brain injury, in general, as most sport-related concussion patients do not present to the emergency department [40] and sport-related concussions are rarely associated with intracranial lesions [41]. Additional methodological factors could also contribute to the seeming inconsistency between studies. The current study included a large-sample size, well-matched controls, and statistically controlled for several variables known to independently influence brain morphometry (e.g., sex, age, body mass index). It should be noted, however, that other studies in non-sport mild traumatic brain injury patients have also failed to find any association between a single injury and structural changes [18,42].

Another important factor in the current study was the ability to isolate the effects of a single sport-related concussion from the cumulative effects of prior concussion and contact sport exposure. Previous studies have reported significant associations between concussion history and/or contact sport exposure on brain morphometry in collegiate athletes [12–14,43]. Thus, it is possible that structural gray matter changes are only observed in association with repetitive head injury due to the cumulative effects of multiple concussions or repeated exposure to non-concussive head impacts. We cannot, however, rule out the possibility that the 6-month follow-up period in the current study did not extend long enough to capture the long-term effects of a single sport-related concussion. Longitudinal studies following injured athletes across multiple years following injury (e.g., follow-up visits after sport participation) are ongoing.

Limitations

Our findings should not be extended to different age groups, competition levels, other sports not included in this study, or non-sport samples. While matched controls provide an adequate reference for potential injury-related changes in brain morphometry, baseline imaging prior to injury would be more sensitive to subject-specific changes but was not achievable in the current study. Although we include both male and female athletes, the sample of athletes with concussion consisted primarily of male football players. Additional studies are needed to determine potential moderating effects of sex. Recruitment for several post-injury visits was limited to athletes who clinically recovered; thus, results may not generalize to the small subset of athletes that do not recover following injury. Finally, as is common in longitudinal studies, not every athlete completed every scan. The mixed effects models employed, however, account for missingness under the missing at random assumption. Moreover, sensitivity analyses demonstrated that acute symptom severity and duration of symptoms did not differ in injured athletes with missing data compared to those that completed all visits (ps>0.10), suggesting that results were not systematically biased by differences in acute injury.

Conclusion

A single, isolated sport-related concussion has minimal association with macroscopic gray matter structure in the acute through early long-term phases post-injury. Future work investigating subject-specific changes in brain volume that do not assume that concussion affects the same region across all participants is warranted.

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What are the new findings?

- This prospective, multi-site study suggests that a single sport-related concussion has minimal measurable associations with cortical and subcortical gray matter during a 6-month follow-up period.

How might it impact on clinical practice in the future?

- Current results can aid clinicians in counseling patients regarding the potential impact of sport-related concussion on brain structure.

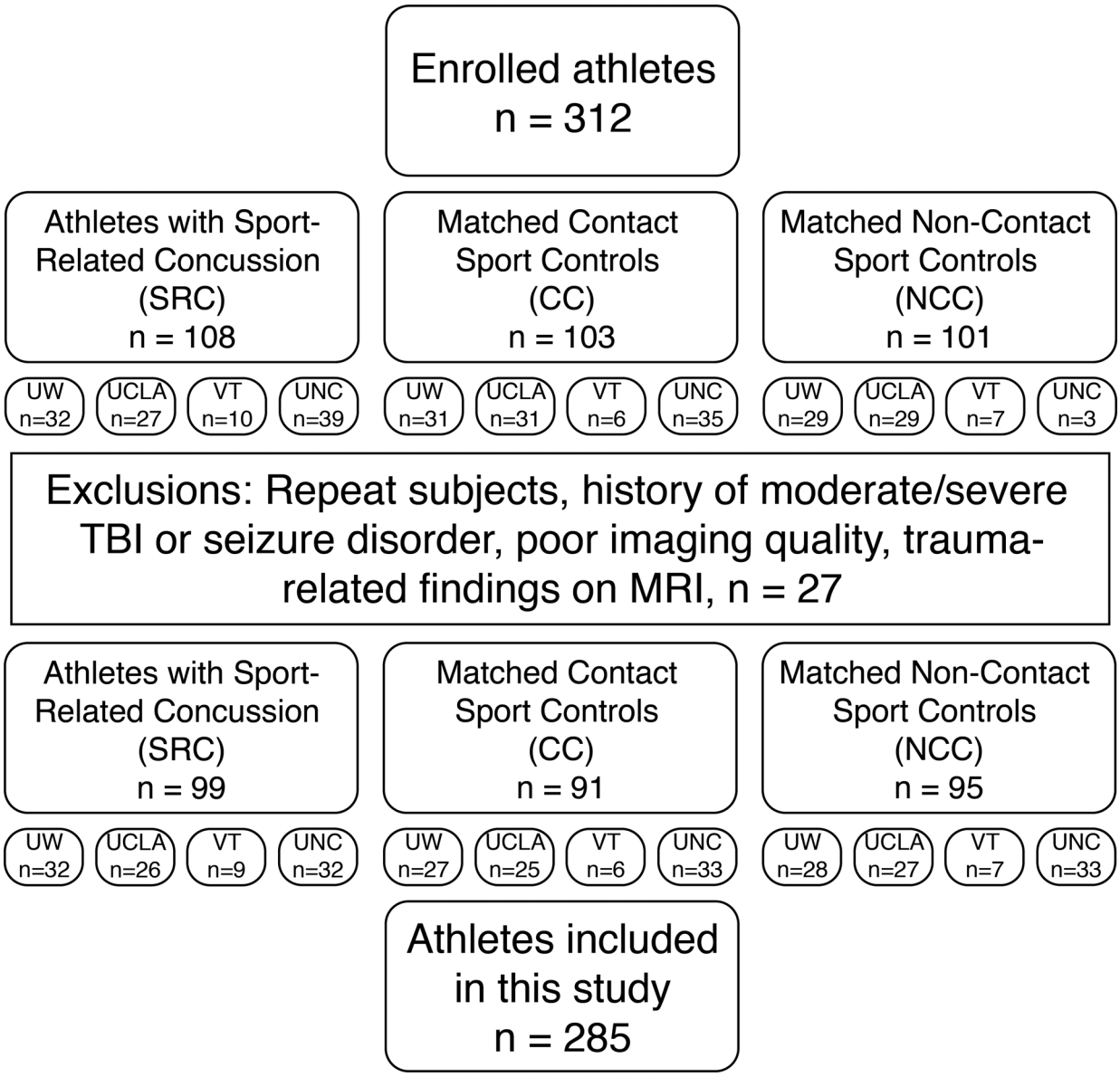

Figure 1: Study enrollment and exclusionary criteria by site

Shown is flow chart indicating athlete enrollment and exclusionary criteria by study site. UW= University of Wisconsin – Madison, UCLA=University of California – Los Angeles, VT-Virginia Tech, and UNC=University of North Carolina at Chapel Hill.

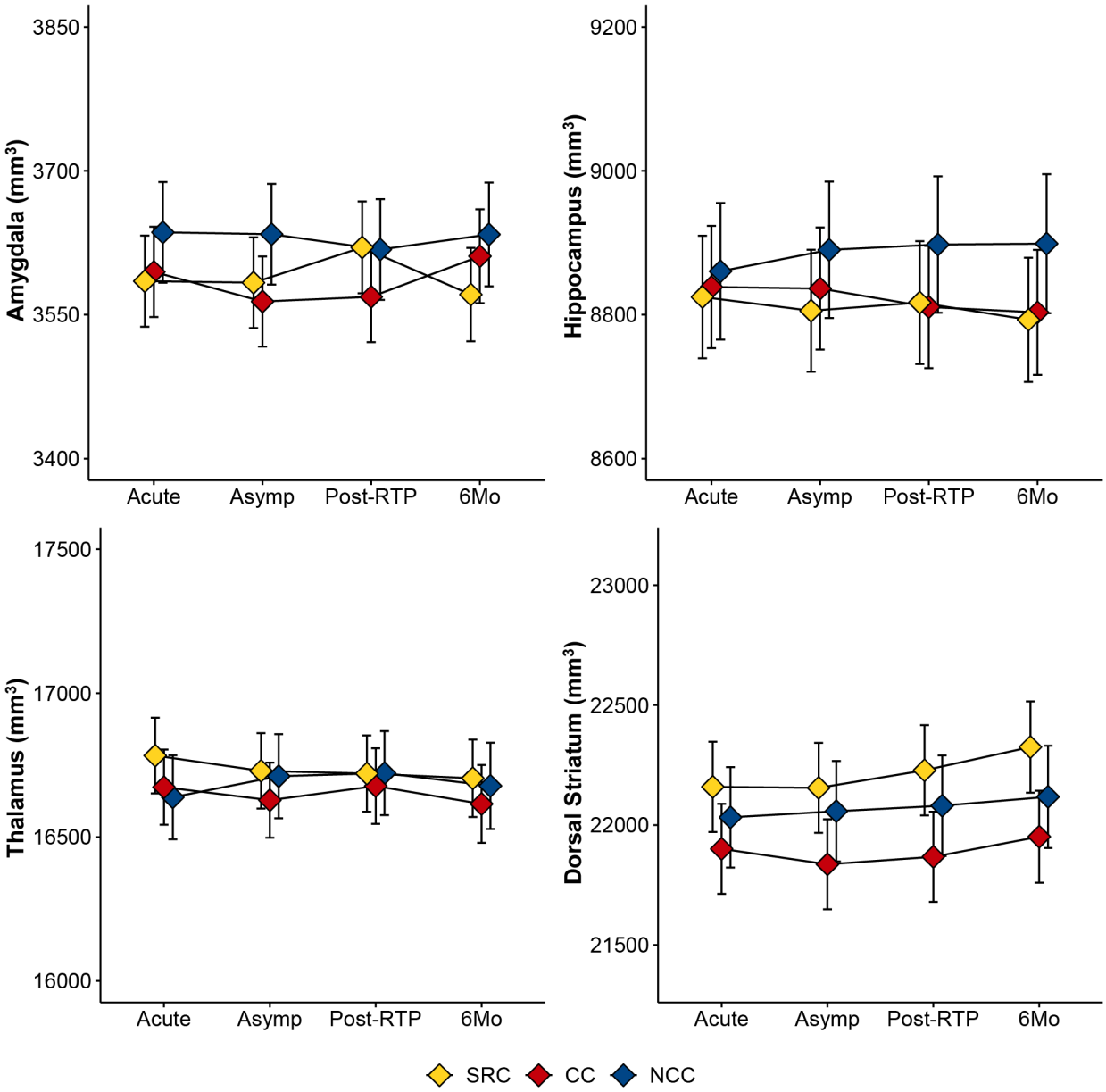

Figure 2: Subcortical volumes in concussed and control participants at each visit

Shown are the marginal means with standard errors for subcortical volumes in athletes with concussion (SRC), contact controls (CC), and non-contact controls at the Acute, Asymptomatic (Asymp), Post-Return-to-Play (Post-RTP), and 6-month (6Mo) visits.

Table 1:

Sample characteristics

Demographics	NCC	CC	SRC	Statistic
Total No.	95	91	99	
No. at each Visit Acute/Asymp./P-RTP/6-month	86/87/88/57	84/87/78/63	76/76/61/60	
Sex (Male/Female)	77/18	71/20	82/17	$X^2(2)=0.72$, p=0.72
Race				Fisher's Exact, p=0.06
White	72	60	61	
Black or African American	12	25	29	
Other	9	4	8	
Unknown/NR	2	2	1	
Ethnicity				$X^2(2)=11.36$, p=0.02
Non-Hispanic	87	77	80	
Hispanic	7	5	5	
Unknown/NR	1	9	14	
Age at Baseline, M(SD)	19.83 (1.19)	19.42 (1.29)	19.29 (1.00)	F(2,282)=5.57, p=0.004
Body mass index, M(SD)	23.48 (3.17)	26.23 (4.16)	27.33 (5.69)	Welch's F(2,179.84)=23.09, p<0.001
WTAR standard score, M(SD)	109.16 (12.59)	109.13 (12.66)	107.55 (13.94)	F(2,233)=0.42, p=0.66
Years Participation at Baseline, M(SD)	10.75 (3.69)	11.09 (3.54)	10.58 (3.74)	F(2.282)=0.48, p=0.62
Sport				$X^2(3)=0.27$, p=0.97[$]
Football	0	51	58	
Ice Hockey	0	8	9	
Lacrosse	0	6	7	
Soccer	0	26	25	
Baseball	34	0	0	
Basketball	11	0	0	
Cross-Country / Track	36	0	0	
Field Event	8	0	0	
Softball	6	0	0	
Previous Concussions				$X^2(2)=23.28$, p<0.001
0	78	62	49	
1 or more	17	29	50	
Scanner/Coil/Site				Fisher's Exact, p=0.76
UW GE MR750	28	27	32	
VT Siemens Trio 8ch	7	6	9	
UNC Siemens Prisma 32ch	25	20	19	
UNC Siemens Trio 12ch	0	1	0	
UNC Siemens Trio 32ch	8	12	13	
UCLA Siemens Prisma 32ch	24	19	16	

Demographics	NCC	CC	SRC	Statistic
UCLA Siemens Trio 12ch	2	4	6	
UCLA Siemens Trio 32ch	1	2	4	
Clinical History				
ADHD	2	6	14	Fisher's Exact, p=0.007
Migraines	4	7	8	Fisher's Exact, p=0.50
Learning Disorder	2	1	3	Fisher's Exact, p=0.87
Memory Disorder	0	2	3	Fisher's Exact, p=0.29
Balance Disorder	0	0	1	Fisher's Exact, p=1.00
Sleep Disorder	1	0	2	Fisher's Exact, p=0.78
Meningitis	0	2	0	Fisher's Exact, p=0.10
Diabetes	0	0	2	Fisher's Exact, p=0.33
Hearing Problems	0	0	2	Fisher's Exact, p=0.33
Vision Problems	0	1	0	Fisher's Exact, p=0.32
Psychiatric Disorder	6	3	4	Fisher's Exact, p=0.60
Injury Information		**CC**	**SRC**	**Statistic**
Acute symptom severity, M(SD)	2.93 (4.59)	3.36 (5.59)	23.09 (18.90)	Welch's F(2,138.15)=40.63, p<0.001
Time to Asymptomatic in Days, M(SD)	N/A	N/A	9.23 (6.04)	N/A
Time to Return-to-Play in Days, M(SD)	N/A	N/A	15.72 (11.21)	N/A
Loss of Consciousness	N/A	N/A	3	N/A
Post-Traumatic Amnesia	N/A	N/A	10	N/A
Retrograde Amnesia	N/A	N/A	8	N/A

Note: Asymp. = Asymptomatic, P-RTP = Post-Return-to-Play, NCC = non-contact control, CC = contact control, SRC = sport-related concussion, No. = number, NR = not reported, M(SD) = mean(standard deviation), UW = University of Wisconsin-Madison, VT = Virginia Tech, UNC = University of North Carolina at Chapel Hill, UCLA = University of California Los Angeles, GE = General Electric, ch = channel, ADHD = attention deficit hyperactivity disorder, N/A = not applicable, $ indicates that statistical comparison was limited to CC and SRC.

Table 2:

Subcortical volumes and associated statistical values for primary analyses

	Acute	Asymp.	P-RTP	6-month	Group Effect	Group-by-Visit
Thalamus						
NCC M(SE)	16,638.18 (146.12)	16,711.38 (146.03)	16,722.03 (146.05)	16,677.80 (149.76)	F(2,273.12)=0.17, p=0.84	F(6,613.90)=1.30, p=0.26
CC M(SE)	16,673.30 (130.74)	16,628.05 (130.65)	16,677.13 (131.18)	16,614.92 (135.39)		
SRC M(SE)	16,782.95 (131.62)	16,729.84 (131.00)	16,720.56 (132.52)	16,704.18 (134.45)		
Hippocampus						
NCC M(SE)	8,860.38 (94.88)	8,890.17 (94.86)	8,897.55 (94.88)	8,898.77 (96.60)	F(2,273.62)=0.29, p=0.75	F(6,610.37)=1.81, p=0.10
CC M(SE))	8,838.50 (84.92)	8,836.43 (84.90)	8,810.72 (85.06)	8,803.27 (86.95)		
SRC M(SE)	8,824.63 (85.18)	8,805.52 (84.87)	8,816.89 (85.34)	8,793.01 (86.27)		
Amygdala						
NCC M(SE)	3,635.89 (52.50)	3,633.92 (52.45)	3,617.98 (52.45)	3,633.68 (54.00)	F(2,270.09)=0.41, p=0.66	F(6,613.19)=2.20, p=0.04
CC M(SE)	3,594.67 (47.01)	3,563.78 (46.96)	3,568.65 (47.21)	3,610.98 (48.97)		
SRC M(SE)	3,585.00 (47.46)	3,583.40 (47.23)	3,620.19 (47.93)	3,570.97 (48.66)		
Dorsal Striatum						
NCC M(SE)	22,032.13 (209.53)	22,057.57 (209.50)	22,080.63 (209.56)	22,117.67 (213.22)	F(2,274.70)=1.11, p=0.33	F(6,611.05)=1.17, p=0.32
CC M(SE))	21,900.68 (187.56)	21,836.28 (187.53)	21,867.46 (187.85)	21,951.32 (191.83)		
SRC M(SE)	22,159.16 (188.11)	22,155.01 (187.46)	22,228.20 (188.39)	22,325.23 (190.32)		

Note: Subcortical volumes are presented as mm^3 in 1 mm isotropic voxel space. Asymp. = Asymptomatic, P-RTP = Post-Return-to-Play, NCC = non-contact control, CC = contact control, SRC = sport-related concussion, M(SE) = Marginal Mean (Standard Error). Underlined values indicate p-values <0.05.

Table 3:

Pairwise comparisons for the amygdalae group-by-visit interaction

Group	Simple Effect of Visit	Pairwise Comparison	MD	SE	df	Sig	95% CI - Lower	95% CI - Upper
CC	F(3, 658.69)=2.49, p=0.06	*6-month vs. P-RTP*	42.33	21.04	729.90	0.045	1.03	83.63
		6-month vs. Asymp.	47.20	20.72	757.83	0.023	6.53	87.87
		6-month vs. Acute	16.30	21.13	768.05	0.44	−25.18	57.78
		P-RTP vs. Asymp.	4.87	17.86	607.27	0.79	−30.21	39.95
		P-RTP vs. Acute	−26.02	18.16	610.78	0.15	−61.69	9.64
		Asymp. vs. Acute	−30.90	17.37	605.18	0.08	−65.01	3.22
SRC	F(3,674.941)=1.82, p=0.14	*6-month vs. P-RTP*	−49.22	22.99	738.41	0.033	−94.36	−4.09
		6-month vs. Asymp.	−12.43	22.27	778.77	0.58	−56.15	31.29
		6-month vs. Acute	−14.03	22.79	781.82	0.54	−58.77	30.71
		P-RTP vs. Asymp.	36.79	20.67	617.85	0.08	−3.80	77.38
		P-RTP vs. Acute	35.19	21.30	623.55	0.10	−6.63	77.02
		Asymp. vs. Acute	−1.60	19.90	624.29	0.94	−40.69	37.49
NCC	F(3,652.31)=0.45, p=0.72	*6-month vs. P-RTP*	15.69	20.78	707.06	0.45	−25.11	56.49
		6-month vs. Asymp.	−0.24	20.98	732.08	0.99	−41.42	40.94
		6-month vs. Acute	−2.22	21.39	740.92	0.92	−44.20	39.77
		P-RTP vs. Asymp.	−15.93	17.30	609.56	0.36	−49.91	18.04
		P-RTP vs. Acute	−17.91	17.51	613.22	0.31	−52.30	16.48
		Asymp. vs. Acute	−1.98	17.48	607.73	0.91	−36.31	32.36

Note: Asymp. = Asymptomatic, P-RTP = Post-Return-to-Play, NCC = non-contact control, CC = contact control, SRC = sport-related concussion, MD = marginal mean difference, SE = Standard Error, df = degrees of freedom, CI = confidence interval, lower = lower bound, upper = upper bound. Differences are in mm^3.