Longitudinal Alterations of Cerebral Blood Flow in High-Contact Sports

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Objective: Repetitive head trauma is common in high-contact sports. Cerebral blood flow (CBF) can measure changes in brain perfusion that could indicate injury. Longitudinal studies with a control group are necessary to account for interindividual and developmental effects. We investigated whether exposure to head impacts causes longitudinal CBF changes.

Methods: We prospectively studied 63 American football (high-contact cohort) and 34 volleyball (low-contact controls) male collegiate athletes, tracking CBF using 3D pseudocontinuous arterial spin labeling magnetic resonance imaging for up to 4 years. Regional relative CBF (rCBF, normalized to cerebellar CBF) was computed after co-registering to T1-weighted images. A linear mixed effects model assessed the relationship of rCBF to sport, time, and their interaction. Within football players, we modeled rCBF against position-based head impact risk and baseline Standardized Concussion Assessment Tool score. Additionally, we evaluated early (1–5 days) and delayed (3–6 months) post-concussion rCBF changes (in-study concussion).

Results: Supratentorial gray matter rCBF declined in football compared with volleyball (sport-time interaction $p = 0.012$), with a strong effect in the parietal lobe ($p = 0.002$). Football players with higher position-based impact-risk had lower occipital rCBF over time (interaction $p = 0.005$), whereas players with lower baseline Standardized Concussion Assessment Tool score (worse performance) had relatively decreased rCBF in the cingulate-insula over time (interaction effect $p = 0.007$). Both cohorts showed a left–right rCBF asymmetry that decreased over time. Football players with an in-study concussion showed an early increase in occipital lobe rCBF ($p = 0.0166$).

Interpretation: These results suggest head impacts may result in an early increase in rCBF, but cumulatively a long-term decrease in rCBF.

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Introduction

Athletes participating in high-contact sports, such as American football, are exposed to a large number of repeated head impacts in a season and during their career.[1,2] Increasing evidence suggests cumulative impacts are associated with persistent neurological impairments,[3,4] cognitive and memory decline,[5,6] and higher risk for chronic traumatic encephalopathy.[7]

Cerebral blood flow (CBF) is closely coupled with brain function. One can measure CBF using modalities, such as position emission tomography, single-photon emission computed tomography, computed tomography, ultrasound, and optical imaging,[8] although these methods have limited coverage or radiation. Magnetic resonance imaging (MRI) can be used for non-invasive CBF estimation, in particular utilizing arterial spin labeling (ASL).

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ASL labels arterial blood water as an endogenous contrast tracer without radiation. By measuring signal with and without labeling, one can quantify CBF with high efficiency.[9]

CBF is altered early in concussion and mild traumatic brain injury (mTBI),[10–14] and changes may persist months after clinical symptoms subside.[11,15] To link neuroimaging with behavior, CBF changes after concussion may be correlated with cognitive tests measured using tools, such as Standardized Concussion Assessment Tool (SCAT),[13] which is widely used for the clinical assessment of concussion in sport. CBF may also be sensitive to subconcussive impacts (subconcussive: impacts that do not cause a clinical concussion, yet may be high velocity), as demonstrated after one season of high-contact sports.[16,17] Such CBF measurements may represent changes in metabolic demand in response to head injury in animal[18] and human studies.[19] Proposed mechanisms include direct damage to brain parenchyma and blood vessels, change in microvasculature structure, and impairment of cerebral autoregulation.[20] Understanding physiological/metabolic changes in response to early/late injury via CBF may provide complementary information to diffusion microstructural techniques.[21]

Cerebral blood flow undergoes changes throughout the lifespan.[22,23] Cumulative head impacts may alter this trajectory. Prior research on sports were cross-sectional studies or spanned only a single sports season. Cross-sectional studies are limited due to high interindividual variability in brain anatomy/perfusion, obscuring subtle changes that may be associated with head impacts. No studies have tracked athletes over years to provide multi-year longitudinal trajectories. One study over a season of high-contact sports found decreased regional CBF in football players with more subconcussive impacts,[17] whereas another found a significant increase in global CBF.[16] Differing conclusions may be related to several variables, such as impact heterogeneity, cohort size, study duration, and developmental effects, suggesting a potential benefit to longitudinal imaging of a cohort, including controls to help disentangle maturational CBF changes.

In addition to longitudinal changes, early CBF changes after concussion could potentially inform clinical decision-making and management. Only a few studies have reported early effects from sport-related concussions in high-impact sports compared with a control group showing elevated CBF in the early phase of concussion.[14,24] Comparison with reference to baseline MRI scans before concussive events could improve detection of early CBF changes. Overall, the cumulative effects of sport-related head impacts remain inadequately understood. Our goal was to investigate whether high-impact sports are associated with longitudinal CBF changes, while accounting for baseline differences and developmental trajectories. We investigate CBF alterations over multiple years in a population of high-contact (football) athletes who are exposed to both concussive and subconcussive impacts, in comparison with low-contact (volleyball) athletes. Volleyball athletes were chosen as an athletic control due to the relatively low-contact nature of play. Using ASL, we tracked 97 collegiate athletes up to 4 years, collecting 315 total MRI scans, including baseline, annual, and postconcussive scans. In addition, we investigated the associations between CBF changes with football players' position-associated impact risk, baseline SCAT score (which measures cognition, coordination, and balance), history of concussion, and years of prior football experience. Furthermore, some of the football players experienced in-study concussions. Therefore, we also report a comparison of MRI scans collected 1–5 days after concussion (early postconcussion) and 3–6 months (delayed postconcussion) with their closest baseline or annual MRI scan before concussion.

Methods

Study Participants

We enrolled 63 high-impact (football [FB]) and 34 low-impact (volleyball [VB]) collegiate male players (Fig 1A) with approval of the Stanford Institutional Review Board (IRB 7, Assurance: FWA00000935), and in accordance with the Health Insurance Portability and Accountability Act, and with informed consent in writing. Inclusion criteria were active participation in FB/VB. Exclusion criteria before enrollment were a self-reported history of severe brain injury, brain surgery, or major psychiatric, neurological, or substance abuse diagnoses. Our team presented the study to the athletes, and we enrolled all eligible athletes who volunteered. MRIs were inspected by a board- and Certificates of Added Qualification-certified neuroradiologist for quality control and to identify incidental findings. Athletes were scanned at the beginning of each athletic season, after concussion within both 1 to 5 days (early post-concussion) and 3 to 6 months (delayed post-concussion), and after their last season of sport participation. In addition, athletes recruited in the first year of the study underwent an extra MRI at season's conclusion.

For all participants, we obtained the timing and number of past concussions self-reported by the athletes and recorded by the trainers, as well as the total duration in years of playing FB before enrollment. FB athletes underwent pre-first-season SCAT testing (versions 2 and 3),[25] and provided their current player position. The SCAT evaluation included the cognitive assessment (orientation,

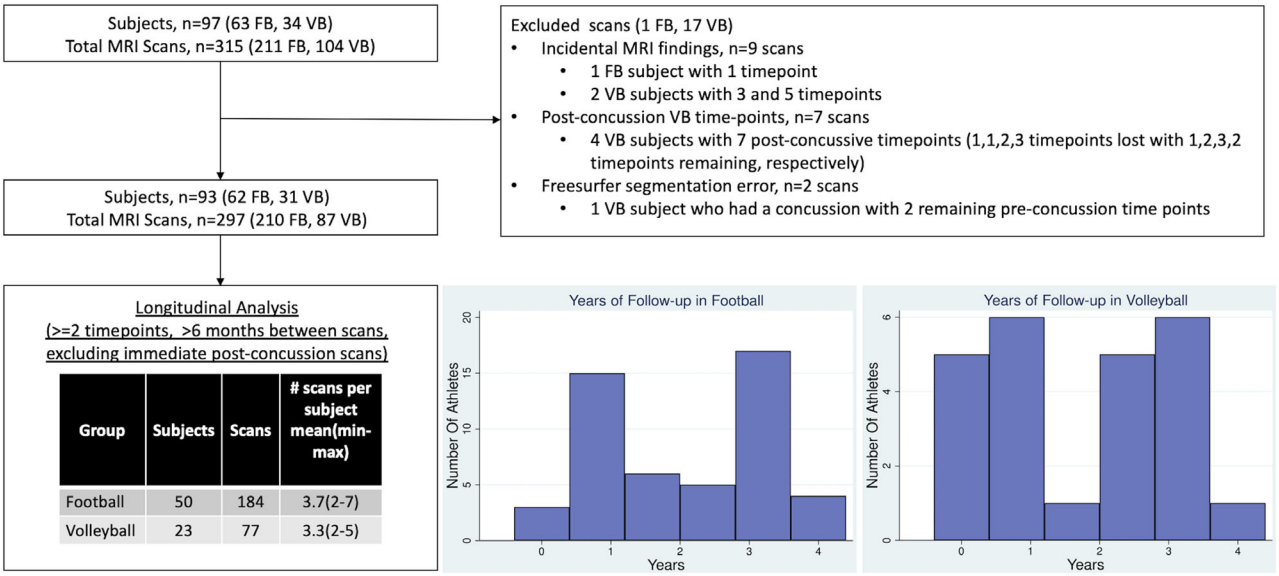

FIGURE 1: Study enrollment showing exclusion criteria and final longitudinal analyses sample size. Bottom right: Distribution of years of follow-up in the 50 football (FB)/23 volleyball (VB) athletes included in the study analysis. MRI, magnetic resonance imaging.

immediate memory, concentration, and delayed recall), balance, and coordination examination portions of the SCAT 2/3 (maximum score: 61). SCAT was unavailable for VB athletes.

Each athlete had from 1 up to 8 MRI scans. Maximum follow-up in the study was 4 years (Fig 1). One FB and 2 VB players (with a total of 9 time points) were excluded due to incidental findings. One VB player had imaging data that could not be adequately postprocessed, which resulted in the exclusion of their 2 MRI scans. Finally, athletes were only included in the longitudinal analysis if they had ≥2 time points at least 6 months apart. The final cohort included 50 FB and 23 VB athletes with 184 and 77 scans, respectively, for the longitudinal analyses, exclusive of in-study concussive scans.

Concussions were identified by the athletic trainers and team physicians. A total of 13 concussions with available early postconcussion scans occurred in 12 FB players during the study, all without loss of consciousness. One FB player had 2 in-study concussions and subsequent postconcussion scans; the second concussion was more severe without a return to play, and was used for the concussion-specific analysis. One of the 12 players only enrolled after a concussion, so their postconcussion scan was their first scan, and their subsequent follow-up (2.5 months later) served as a baseline scan. To increase the number of participants in this concussive cohort, we accessed an additional separate cohort of FB players. Specifically, we reviewed that additional cohort for all participants that fit our concussion analysis criteria (collegiate male FB players from the same institution with baseline and early post-concussion imaging). We included all additional FB players that met these criteria (2 in total); these were added only to the concussion analyses in this study, resulting in a total 14 athletes with post-concussive MRI scans. Four of the VB athletes had in-study concussions (n = 7 post concussive time points), these were excluded to eliminate the effects of concussion on our control cohort.

Image Acquisition

All imaging was conducted using a research-dedicated whole-body 3-T MRI system (MR750; GE Healthcare, Milwaukee, WI, USA), with an 8-channel receive-only head coil. All scans were carried out on the same scanner, except for 8 scans on 3 participants who did not experience a concussion within the study. Excluding these scans did not change the significance of any key results. Participants were instructed not to consume caffeine in the 6 h before MRI.

Anatomical MRI was performed using a whole brain T1-weighted inversion recovery fast spoiled gradient echo sequence (axial, TR = 7.9 ms, TE = 3.1 ms, number of excitations NEX = 1, voxel size = 1 mm isotropic, field of view = 24 cm, matrix size 24 × 24, 182 slices [1-mm thickness], duration = 5 min).

Arterial spin labeling MRI was performed using a pseudo-continuous ASL sequence: 3D fast spin-echo pCASL, field of view 24 cm, NEX = 3, labeling/bolus duration = 1.45 s, 512 time points, 8 arms, post-label delay 2.025 s, voxel size = 2 × 2 × 4 mm,[3] duration = 5 min, and a simultaneously acquired proton density image with TR = 2 s used for the purpose of quantification. The ASL labeling plane was placed at the inferior aspect of the

cerebellum, ensuring the entire cerebellum was covered for this scan.

FreeSurfer Segmentation

Segmentation of T1 images was performed using the FreeSurfer version 5.3 longitudinal pipeline (http://surfer.nmr.mgh.harvard.edu/),[26] as reported on these participants in our previous work.[27]

Cerebral Blood Flow Calculation

Figure 2A shows a block diagram for CBF computation and segmentation. ASL difference images were co-registered to each participant's FreeSurfer-processed T1 image using a boundary-based cost function,[28] which was reviewed for accuracy blind to participant identity and concussion status. A binary mask of the brain in FreeSurfer space was registered to ASL space using the inverse transformation. ASL difference images were divided by GE scanners global scaling factor of 32, and then number of excitations (NEX) 3 to compute mean ASL label/control difference image (ASL_{diff}). The simultaneously acquired proton density image was used to compute equilibrium magnetization of arterial blood on a voxel-by-voxel basis. To compensate for T1 relaxation, the proton density image was multiplied by a correction factor of $(1/1-e^{-\mathrm{TR}/\mathrm{T1}_{\mathrm{Tissue}}})$.[9] $T1_{Tissue}$ was assumed to be the T1 of the gray matter (1.3 s at 3 T). To compute equilibrium magnetization of arterial blood (M_{0a}) from the corrected proton density image, the brain/blood partition coefficient (λ) was assumed to be 90%.[9] After masking using the FreeSurfer space brain mask, partial volume effects at the edges of the brain were corrected by eroding and extrapolating M_{0a} using the Oxford ASL toolbox, asl_file command (with the extrapolation option), followed by median filtering. CBF was then computed using the following equation:[9]

$$CBF = \frac{6000 \cdot \lambda \cdot ASL_{diff} \cdot e^{\frac{PLD}{T1_{blood}}}}{2 \cdot \alpha \cdot T1_{blood} \cdot M_{0a} \cdot \left(1 - e^{-\frac{\tau}{T1_{blood}}}\right) \cdot BackSupp} [ml/100\,g/min]$$

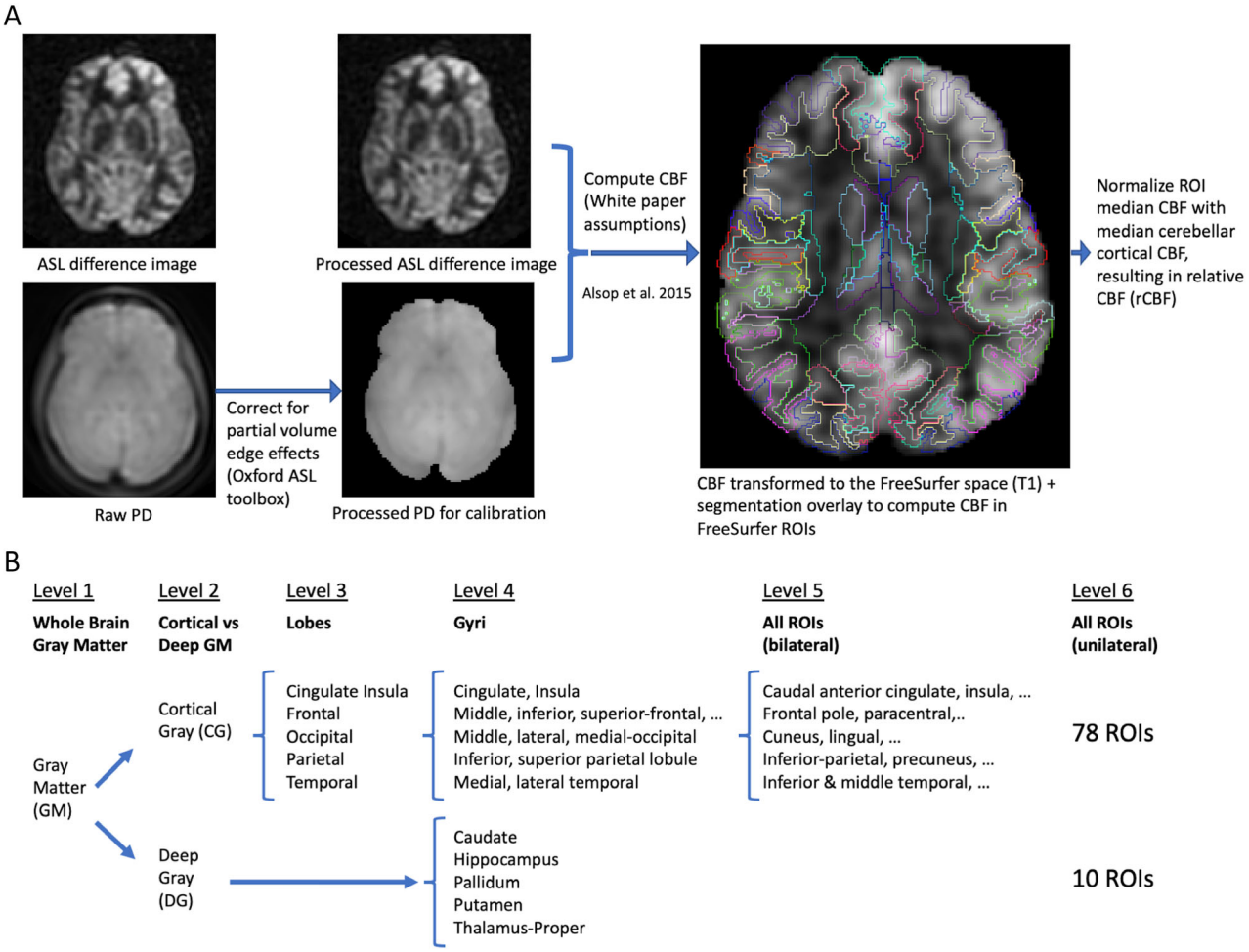

FIGURE 2: (A) Cerebral blood flow (CBF) computation and FreeSurfer segmentation. (B) Hierarchical structure of regions of interest (ROIs) across the brain. ASL, arterial spin labeling; CG, cortical gray; DG, deep gray; GM, gray matter.

where PLD is the postlabeling delay (2.025 s), $T1_{blood}$ is the longitudinal relaxation time of blood (1.65 s at 3 T),[9] τ is the bolus duration (1.45 s), α is the labeling efficacy for pCASL (0.8), and *BackSupp* is the effective background suppression factor for the sequence (0.75).[29]

CBF maps were then transformed to the FreeSurfer space to compute regional perfusion in each FreeSurfer segmented region of interest (ROI). To account for inter-scan variability in global CBF, we computed relative CBF (rCBF) by normalizing each participant's CBF values in each ROI with median cerebellar cortical CBF. This adjusts for variations in ASL signal associated with scanner and physiological variance, which is a necessary step to reduce noise and increase detection power.[30] We used the cerebellum for normalization given that it is rarely affected in mTBI[31] and that this enables assessment of the supratentorial structures of interest, and as such, it is commonly used in other forms of metabolic and perfusion imaging.[32] We only analyzed perfusion in gray matter (not white matter due to its low CBF),[30] taking the median across each FreeSurfer gray matter ROI. All CBF scans were quality controlled for a second time after computing CBF, ensuring image quality and coverage of the cerebellum in all participants included in the analyses. To evaluate CBF in a top-down fashion; that is, starting with whole brain rCBF, then a more granular level using single ROIs, we created a hierarchical structure of ROIs across the brain, in each level averaging the CBF of aggregated regions, weighted by their volume (Fig 2B). These levels included: (1) all gray matter: combining all ROIs across cortex and deep gray (except cerebellum); (2) cortical versus deep gray: two ROIs, one across the whole cortex, and the other across all deep gray structures; (3) lobar ROIs: combined gyri across lobes and hemispheres; (4) gyral ROIs: combined cortical ROIs within gyri and across hemispheres; (5) bilateral: combined left and right ROIs; and (6) single ROIs: separate left and right ROIs.

Statistics

Demographics variables at baseline were compared between the two athlete groups using the Wilcoxon rank-sum and Fisher's exact tests (Table 1). Age at baseline, body mass index, and race were significantly different between the two cohorts. Although these did not significantly contribute to the linear mixed effects (LME) model below when tested by a likelihood ratio test, we included them in the model below for completeness.

An LME model was used in Stata (V15.0; StataCorp LP, College Station, TX, USA; http://www.stata.com) to investigate the longitudinal rCBF changes in each ROI. The LME model included participants as random effects and the following fixed effects: sport (FB coded as 1 and VB as 0), time, and the interaction between sport and time, using a robust standard error estimate (with the vce(robust) option). rCBF data were tested for normality globally using skewness and kurtosis tests of regression residuals.[33] The resulting *p*-values for each effect were considered significant if they passed a multiple comparison correction threshold[34] associated with the ROIs within each level, separately for levels 2 through 6 in our parcellation hierarchy (top level 1 refers to all gray matter and was not corrected). This method estimates the number of independent tests performed by computing the eigenvalues of the level's correlation matrix. The adjusted *p*-values (thresholds) were as follows: level 2: 0.025 deep gray and cortical gray; level 3: 0.017 combined gyri across lobes; level 4: 0.009 combined cortical ROIs within gyri; level 5: 0.004 combined left and right ROIs; and level 6:

TABLE 1. Baseline Demographics of the Participant Population

Demographics variable At baseline	Football ($N = 50$) Median (range)	Volleyball ($N = 23$) Median (range)	*p*-value
Age at baseline (years)	18.7 (17.6, 27.2)	19.2 (18.3, 21.3)	0.001
Body mass index	29.2 (21.7, 38.2)	23.1 (19.9, 26.5)	<0.001
Years of tackle football	9 (4, 14)	0 (0, 1)	<0.001
SCAT with/without concussion	55 (51, 61)/54.5 (42, 61)		0.653
White race	21/50 (42%)	18/23 (78%)	0.005
Prior concussions	16/50 (32%)	2/23 (8.6%)	0.041

Abbreviations: SCAT, Standardized Concussion Assessment Tool.

0.002 for single ROIs. Early postconcussive scans (within 1–5 days after concussion) were not included in the longitudinal analysis to focus on long-term changes and avoid potential transient effects that we would explore separately. All subsequent time points (including 3–6 month delayed postconcussion scans, and any annual follow-up MRIs) were well after resolution of concussion symptoms and return to play, and were hence included.

Within Football Analyses

We performed separate analyses to investigate the effects of four different behavioral and sport-related variables on rCBF changes exclusively within FB. First, literature-derived impact risk associated with player position, HITsp, which is a weighted composite measure of linear and rotational accelerations, impact duration, and location that quantifies head impacts severity.[35] Crisco et al. found a strong association between head impact magnitude and player's position, which more accurately quantifies the severity of impacts based on athlete's position.[36] Second, years of playing tackle FB. Third, history of concussion (either before study enrollment and/or occurring within the timeframe of this study). Fourth, baseline SCAT scores. Separate linear mixed effects models were used to test whether each of these variables or their interaction with time was related to rCBF (fixed effects included one of these four covariates, time, and the interaction effect between that covariate and time). A similar multiple comparison correction was performed.

Concussion Analyses

We performed separate analyses to examine early effects of concussion for FB players who had an in-study concussion (n = 14 participants: 12 FB players from the main cohort and two FB players from another cohort of the same institution). Early postconcussive scans (within 1–5 days of injury; median = 1 day; mean = 2 days) were compared with the closest preceding baseline or annual scan (average time between pre- and early postconcussive scans were 106.5 days, range 16–371, median 103, mean 106.5). For one participant, the preconcussion scan was not available, so the delayed postconcussive scan was used as a baseline (2.5 months after concussion). From the other 13 participants, 11 participated in delayed postconcussion scans. The Wilcoxon signed-rank test was used to compare relative CBF values pre-, early, and delayed postconcussion. A similar multiple comparison correction was carried out.

Results

Participant Demographics

Athletes' demographics are shown in Table 1. VB athletes were slightly (2.7%) older compared with FB players (median age at baseline 19.2 vs 18.7, respectively). Body mass index was significantly higher (26.4%) in FB players. A total of 16 FB players and 2 VB players included in the longitudinal analysis had concussions before study enrollment. Two VB players had prior tackle FB experience; however, it was significantly shorter compared with that of FB players (maximum 1 year for VB vs 4–14 years for FB). In FB, there were significantly (46.3%) fewer white players compared with VB (21 out of 50 FB players vs 18 out of 23 VB players). None of these differences in demographics contributed to the LME model. There were no statistically significant differences in baseline SCAT scores between FB players with versus without history of concussion.

Differences in rCBF between Sports

There was a significant group (sport) by time interaction effect at the top level of total gray matter (GM; which includes both cortical and deep gray): GM rCBF declined over time in FB compared with VB ($\beta = -0.021$, $p = 0.012$, n = 50FB/23VB; Fig 3A, Table 2). At more granular hierarchy levels, the same interaction was observed in cortical gray matter ($\beta = -0.022$, $p = 0.013$, Fig 3C), but not deep gray matter ($\beta = -0.011$, $p = 0.203$, Fig 3C). Within the cortex, the parietal lobe showed the strongest interaction ($\beta = -0.028$, $p = 0.002$; Fig 3D). The most involved subregions included the inferior parietal lobe, precuneus, and the paracentral region. Comparing only FB players with a history of any concussion (either before enrollment or during the study) with VB (Fig 3E) showed the same effect in the whole GM (interaction $p = 0.01$, n = 24FB/23VB), but FB players without such a concussive history (Fig 3F) did not differ significantly from VB (interaction $p = 0.233$, n = 26FB/23VB). We should note here that the non-concussed and concussed cohorts are not themselves statistically different over time (interaction $p = 0.499$, n = 24FB with concussion history/26 FB without concussion history).

Examining differences in sports separate from time (ie, a group effect of sport), rCBF was higher in FB compared with VB in all GM ($\beta = 0.06$, $p = 0.005$, n = 50FB/23VB; Fig 3A, Table 2). This effect was localized to cortical gray ($\beta = 0.062$, $p = 0.004$; Fig 3C), but not deep gray matter ($\beta = 0.037$, $p = 0.145$). The effect remained significant in frontal and occipital lobes of the brain (Table 2). Examination of the cerebellar CBF without normalization (Fig 4A) did not show statistically significant group differences in CBF ($\beta = -3.84$, $p = 0.089$). Notably, the cerebellar CBF was stable over time between sports ($\beta = -0.309$, $p < 0.778$), and so could not explain sport-time interactions.

Examining the effect of time separate from sport, there was no difference in whole brain GM rCBF over time ($\beta = 0.005$, $p = 0.403$, n = 50FB/23VB), although the rCBF of parietal and occipital regions increased significantly over time. Notably, in both sports, the ratio of left-to-right

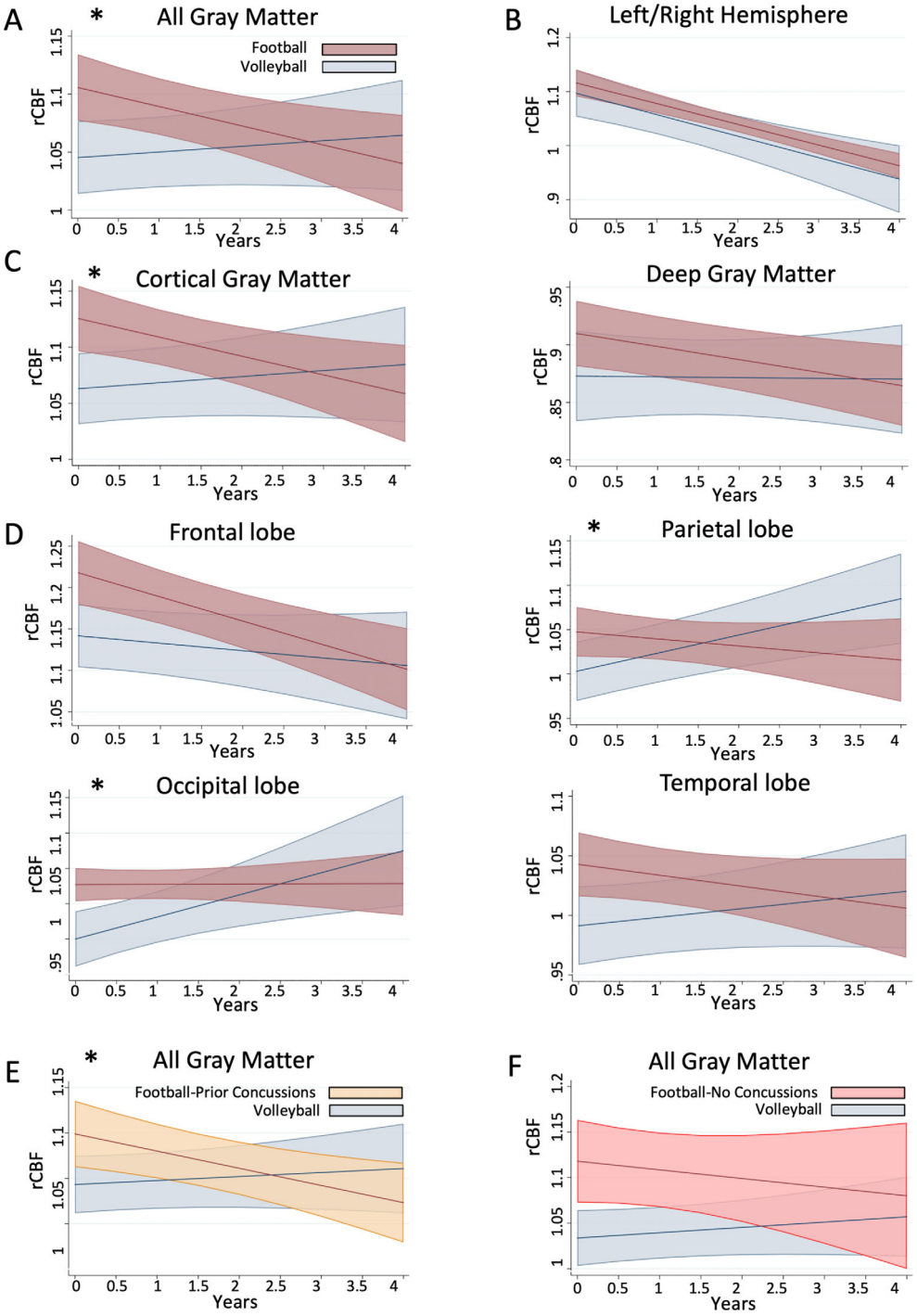

FIGURE 3: Longitudinal changes of relative cerebral blood flow (rCBF). Changing CBF trajectories for football (red) and volleyball (blue). (A) Level 1: all gray matter. (B) Level 2, gray matter separated by hemisphere. (C) Level 2: cortical gray and deep gray matter. (D) Level 3, brain lobes. (E) All gray matter rCBF in football players with prior history of concussion versus volleyball. (F) All gray matter rCBF in football players with no history of concussion versus volleyball. *Indicates significant interaction effects (representing a relative reduction in rCBF in football compared with volleyball) after multiple comparison correction.

hemisphere GM rCBF significantly declined over time ($\beta = -0.04$, $p < 0.001$; Fig 3B, Table 2). This left-to-right ratio showed no difference between sports ($\beta = 0.019$, $p = 0.453$) and no sport-time interaction ($\beta = 0.001$, $p = 0.898$), and was still present without cerebellar normalization ($\beta = -0.039$, $p < 0.001$; Fig 4B).

We had previously reported that longitudinal cortical thinning was attenuated in the same FB cohort compared with VB cohort.[27] To examine a possible contribution of gray matter volume to the rCBF changes found here, we added either total GM volume or thickness into the model as an additional fixed effect. Neither

TABLE 2. Statistical Difference of Relative Cerebral Blood Flow Between Sports

	Group effect		Time effect		Interaction effect	
	p-value	ΔrCBF between sports (95% CI)	*p*-value	ΔrCBF per year (95% CI)	*p*-value	ΔrCBF/year between sports (95% CI)
LEVEL 1						
All gray matter	**0.005**[a]	0.06 (0.018, 0.103)	0.403	0.005 (−0.006, 0.016)	**0.012**[a]	−0.021 (−0.038, −0.005)
LEVEL 2						
Cortical gray	**0.004**[a]	0.062 (0.019, 0.105)	0.383	0.005 (−0.007, 0.017)	**0.013**[a]	−0.022 (−0.04, −0.005)
Deep gray	0.145	0.037 (−0.013, 0.087)	0.925	−0.001 (−0.015, 0.013)	0.203	−0.011 (−0.027, 0.006)
LEVEL 3						
Cingulate insula	0.075	0.057 (−0.006, 0.119)	0.34	−0.008 (−0.026, 0.009)	0.203	−0.015 (−0.037, 0.008)
Frontal	**0.007**[a]	0.076 (0.021, 0.131)	0.242	−0.009 (−0.024, 0.006)	0.059	−0.02 (−0.041, 0.001)
Occipital	**0.001**[a]	0.077 (0.03, 0.123)	**0.004**[a]	0.031 (0.01, 0.053)	**0.015**[a]	−0.031 (−0.056, −0.006)
Parietal	0.039	0.044 (0.002, 0.087)	**<0.001**[a]	0.02 (0.009, 0.032)	**0.002**[a]	−0.028 (−0.046, −0.011)
Temporal	0.021	0.051 (0.008, 0.095)	0.252	0.007 (−0.005, 0.02)	0.061	−0.016 (−0.034, 0.001)
Left/right hemisphere	0.453	0.019 (−0.031, 0.069)	**<0.001**[a]	−0.04 (−0.059, −0.021)	0.898	0.001 (−0.02, 0.022)

[a]Indicates significant effects after multiple comparison correction.
Abbreviations: rCBF = relative cerebral blood flow.

total GM volume nor thickness contributed to the model ($p = 0.375$ and $p = 0.859$, respectively), and neither total GM volume nor thickness were associated with rCBF changes ($p = 0.205$ and $p = 0.8593$, respectively).

Within Football Analyses

Whole brain GM rCBF did not have a statistically significant association with position-associated impact risk (HITsp). The median value of HITsp was computed (median HITsp = 31). FB players with HITsp value above/below 31 were in the high/low HITsp group. At level 3 (brain lobes), FB players with higher impact risk measured at baseline (high HITsp) had a relatively decreased rCBF over time (up to 4 years) in the occipital lobe (interaction effect: $p = 0.005$, n = 19, high FB/31 lowFB; Fig 5A–C). Similarly, all GM rCBF did not have a statistically significant association with SCAT score at baseline. However, FB players with a lower SCAT score

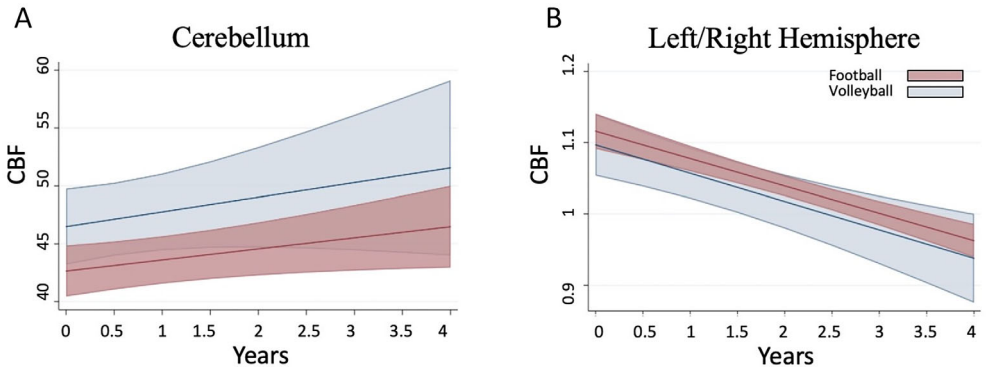

FIGURE 4: Longitudinal changes of cerebral blood flow (CBF) without normalization to the cerebellum. (A) cerebellum. (B) Left/right hemisphere.

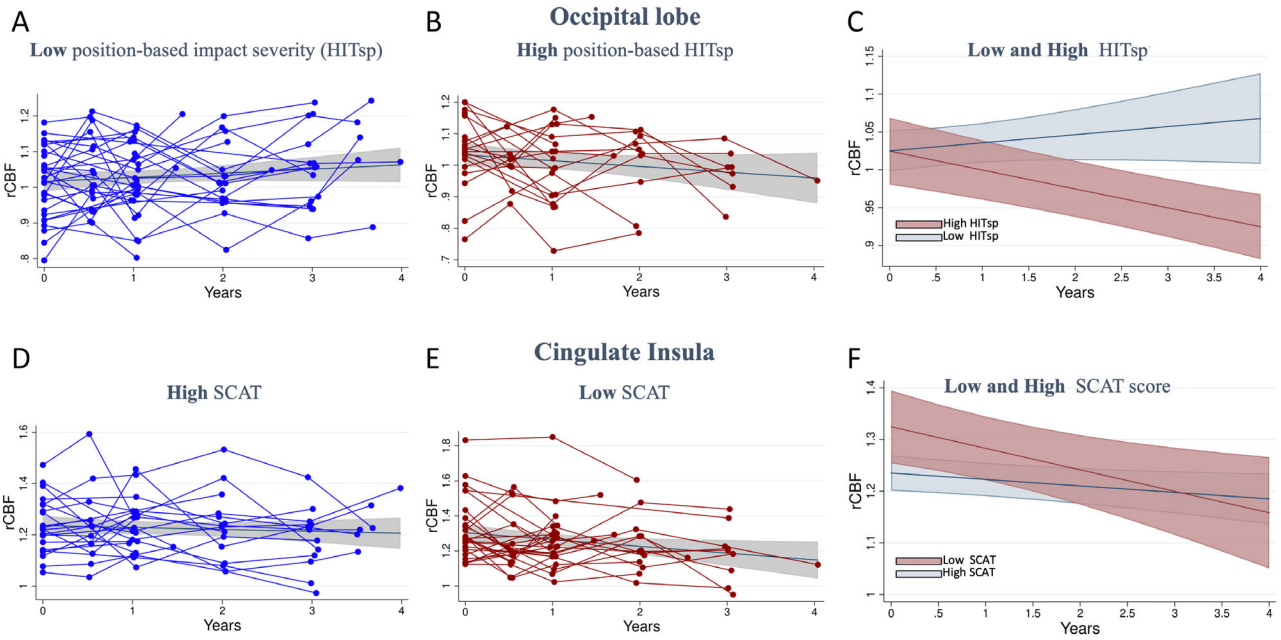

FIGURE 5: Within football analyses. Players with lower position-based impact risk (HITsp) had increased occipital relative cerebral blood flow (rCBF) over time (A) versus players with high HITsp (B). Players with higher Standardized Concussion Assessment Tool (SCAT) score (better performance) had relatively increased rCBF over time in the cingulate-insula (E) compared with players with a low SCAT score (D).

(worse performance) at baseline had relatively lower rCBF in the cingulate-insula over time compared to players with higher SCAT score (interaction effect: $p = 0.007$, n = 28, lowFB/22 highFB; Fig 5D–F). There were no significant interaction effects for years of tackle FB or for the presence of prior or in-study concussions.

Early Effect of Concussion

We examined the early effect of concussion (1–5 days after injury, mean 2 days, median 1 day) for 14 FB players that experienced an in-study concussion with reference to baseline imaging. There were no statistically significant changes in total GM rCBF. However, we observed a significant occipital lobe rCBF increase ($p = 0.0166$, below the correction threshold of 0.0169, n = 14) in the early postconcussion period compared with the most recent prior preconcussion scan (Fig 6). Occipital rCBF at the early versus delayed postconcussion scan (3–6 months) was not significantly different ($p = 0.388$). The preconcussion versus delayed postconcussion occipital rCBF was close to, but did not reach, a statistically significant difference ($p = 0.0186$).

Discussion

The present study investigated longitudinal CBF changes (over 4 years) using arterial spin labeling MRI in a

A

Brain region	Pre vs. early post-concussion *p*-value
Occipital	0.0166*
Parietal	0.855
Frontal	0.426
Temporal	0.714
Cingulate Insula	0.357

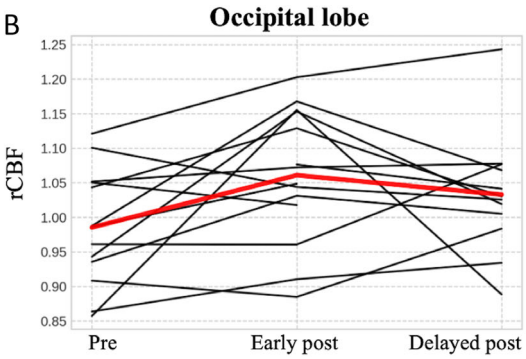

FIGURE 6: Early effects of concussion. (A) Occipital relative cerebral blood flow (rCBF) increased in the early postconcussion period (day 1–5) compared with preconcussion imaging (*significant after multiple comparison correction threshold of 0.0169). (B) Plots showing occipital rCBF at baseline (Pre), 1–5 days after concussion (Early post), and their follow-up magnetic resonance imaging rCBF 3–6 months after concussion (Delayed post) for each athlete (n = 14, the thick red line represents the mean).

population of high-contact sport (FB) college athletes who were exposed to both concussive and subconcussive impacts in comparison with a low-contact cohort (VB). We found a global decline in relative perfusion in FB compared with VB, suggesting an inverse association between impacts and longitudinal perfusion. Along the same lines, FB players with higher impact risk measured at baseline (high HITsp) had decreasing occipital rCBF over time, whereas FB players with lower SCAT score (worse performance) at baseline had decreasing rCBF in the cingulate insula over time. In contrast to the longitudinal findings, concussion resulted in a mild increase in occipital lobe rCBF in the early post-concussive period. Separately, we report the novel finding that a perfusion asymmetry exists in this age group and decreases over time.

Longitudinal Relative CBF Decline in Football

Prior studies have largely either been cross-sectional or tracked athletes over a single season.[17] A study of collegiate FB tracked athletes during one season of high-contact sport, and they found a significant decline in CBF in the parietal lobe in high compared with low exposure FB.[17] We build upon this by demonstrating a parietal rCBF decline in FB over a longer time period and in comparison with a low-contact control cohort, which adds a further comparator of relevance. Slobounov et al. reported a marginally significant ($p = 0.048$) increase in global CBF after a season of college FB.[16] However, that study focused on a single season of 18 participants with no control sport and no normalization of CBF values to counter interscan and interparticipant variability.[16] Utilizing a control population, Churchill et al. tracked concussed athletes 1 year after return to play comparing with a large control cohort of nonconcussed athletes, and they also observed a persistent decrease in CBF 1 year after return to play.[15] It should be noted that despite significant group by time integration effects observed comparing only FB with a history of concussion with VB, and no significant effects in only FB without history of concussions versus VB (Fig 3E, F, respectively), we did not observe any significant difference between FB with versus without a history of concussion. This could potentially be due to low sample size in FB without concussion history cohort and other potential differences between these FB subgroups, limiting the conclusions that can be drawn from this observation.

Our within-FB data similarly support this pattern, with rCBF decreasing over time in those at high-impact risk and those with lower baseline SCAT scores. SCAT is widely used in the clinical assessment of sport-related concussions, and the SCAT cognitive score has been shown to correlate with the number of head impacts sustained (>20 g) during a season of high-impact sports.[37] Other studies correlating SCAT with imaging have shown reduction in CBF 1 year after return to play negatively correlating with SCAT symptom severity,[15] and impaired SCAT cognitive performance 1 day after concussion with elevated CBF compared with day 8 after concussion.[13] None of these studies tracked athletes for multiple years, so given the lack of longitudinal studies in athletes, there is a need for future longitudinal research in athletes correlating CBF changes with neurobehavioral measures, such as SCAT and beyond in this age range. We did not find a correlation between rCBF and the years of prior FB experience, which we speculate could mean that developmental effects and their relationship with CBF changes may reflect more recent exposure.

The underlying mechanisms of reduced CBF following late brain injury is not fully understood. Reduced CBF in late TBI is potentially attributed to altered cerebrovascular autoregulation resulting in regional perfusion imbalances that are often detected remote from the point of impact,[20] and elevated capillary transit time heterogeneity leading to reductions in oxygen availability.[38] In addition, the neurovascular unit attempts to repair itself to achieve homeostasis after injury, and an impaired signaling cascade might induce secondary injury of the neurovascular unit if homeostasis is not restored quickly.[20] Reduced neuronal parenchyma could also be a consideration. We had previously reported reduced longitudinal cortical thinning in FB compared with VB, in the same cohort.[27] We did not find that cortical thinning statistically explained rCBF divergence between FB and VB, suggesting the perfusion effect is independent of cortical thinning. Along the same lines, because cortex is primarily responsible for CBF measurements, reduced cortical thinning would be expected to increase, not decrease, the total CBF. Thinning effects were in the order of 0.5% per year, whereas rCBF changes were larger at approximately 2%. This suggests that our finding is independent of cortical volumetric changes and instead reflects primarily a change in tissue blood flow.

The CBF alterations of normal development have not been thoroughly documented at this age range, although may be inferred from the VB controls. In general, studies that have observed CBF trends over decades have reported that CBF seems to slowly decline with age;[39,40] however, the decrease is very gradual, and the previously reported values in the specific age range of our study seem to be relatively flat.[41] Within that frame, it can be speculated that repetitive impacts occurring in FB contribute to processes that alter the brain's morphology and function, imitating a boosted "aging" process that is faster than non-contact controls.

Left Compared with Right Hemisphere CBF

We observed that the ratio of left-to-right hemisphere rCBF declined over time in both sport groups, with an up to 10% difference. This unexpected finding may reflect developmentally normal physiology. It is known that the brain hemispheres are anatomically and functionally asymmetric. However, the change in this asymmetry with age is not well understood. Amen et al., observed more asymmetric SPECT activity in NFL players compared with a group of control participants;[42] however, they did not perform any longitudinal studies. Given the lack of longitudinal studies in athletes, it is unclear whether our observation is due to aging or physical exercise, or is even an entirely normal finding, representing an opportunity for more longitudinal research in athletes and healthy controls in this age range.

Concussion Analysis

Analyzing 14 participants with in-study concussions, we observed a mild early increase in occipital rCBF compared with baseline. The follow-up rCBF at 3–6 months is not statistically different from either the baseline or early postconcussion scan, suggesting that it may be at an intermediate level, suggesting incomplete normalization. Prior work has similarly found elevated CBF during the early phase (1–7 days) of sport-related concussion in the occipital lobe and cuneus, which was associated with higher symptom severity.[43] Similarly, Lin et al. examined a group of mTBI patients and found patients with more severe symptoms had increased occipital CBF.[44] In addition, Churchill et al. examined a group of concussed athletes (involving FB, rugby, hockey, soccer, lacrosse, basketball, and VB), and found decreased frontal, but elevated posterior cingulate, CBF relative to the mean of control participants (individually matched on age, and prior number of concussions) 1–3 days post injury.[14] Doshi et al. studied mTBI patients within 48 h after injury, and observed an increase in frontal and occipital lobes CBF compared with a control group.[24] In addition, animal studies support hypermetabolism in the acute phase (1–24 h) of brain injury in rats.[18] Thomale et al. studied rats 4 h, 24 h, and 48 h after injury, and they reported hypoperfusion at 4 h related to vasoconstriction and microcirculatory stasis, followed by a long-lasting phase of hyperperfusion at 24 h and 48 h reflected by vasodilation and increased flow velocity in arterioles and venules.[45] Potential mechanisms for this transient increase include vascular smooth muscle dysfunction resulting in vasoparalysis, sustained release of vasodilating mediators, such as nitric oxide, and tissue acidosis.[45] In summary, these findings are consistent with an early vascular reaction in response to injury that causes an increase in local blood flow and oxygen supply.[20] Despite the variability in location of CBF changes, the literature does seem to suggest an increase dependent on the timing.

Early Versus Late Effects

The early and late effects found in the present study show opposite directionalities: rCBF increased locally in the occipital lobe 1–5 days postconcussion, but decreased relative to controls over a later window of a few years in the entire cortical gray matter. This is supported by our follow-up imaging in our concussion cases, where the delayed postconcussive rCBF was not statistically different from baseline. We speculate that concussive and subconcussive impacts cause injury associated with increased rCBF locally in the early phases of injury, but rCBF then presumably recovers (normalizes) to baseline or even lower levels, especially after many of these events. The spatial separation of occipital early increases versus parietal late decreases, observed as well (separately) in prior studies, may suggest a more complex underlying mechanism, such as altered cerebrovascular and even neural networks, and secondary metabolic changes.

Limitations

We only investigated longitudinal rCBF changes in male athletes from the same institution. In the future, we will investigate whether similar findings are observed in female athletes, and include different sports and institutions. A larger longitudinal cohort would be more powerful for discerning subtle changes with more confidence. In addition, we did not quantify head impacts, which could more directly link rCBF to the biomechanics of early or cumulative injury. We attempted to link rCBF to exposure using literature values for frequency of impacts, which entails the unproven assumption that these measures are reflective of the players in our cohort. Future work will include instrumented mouthguards to measure hits to the head to quantify impacts and model their effects. Although our study is longitudinal over several years of play, we could not investigate whether any effects are maintained over a longer term. ASL measurement of CBF is known to be influenced by a number of factors including use of caffeine, physical exercise, mood, nutrition, stress, blood gas levels, instrument technical variability, and so on,[46] which we tried to minimize by evaluating participants longitudinallyand normalizing to cerebellar CBF. In addition, demographics variables, such as intensity of training, time to focus on intellectual education cognitive and/or personality differences, and amount of cardiovascular training, could contribute to rCBF differences observed in the present study. Future work should include collecting these demographics variables and examining their effects on rCBF alterations. Finally, concussive

and subconcussive impacts are not expected to be uniform, and can result in differing locations of brain effects between impacts and players, which would require different techniques to detect and can be the subject of future work.

Conclusion

An observed longitudinal decline in GM rCBF in FB compared with VB players, suggests exposure to cumulative impacts may cause a late rCBF decrease. In contrast, an early increase in occipital rCBF after concussion suggests early vascular changes in response to injury, which are partly sustained after 3–6 months. Future longitudinal studies involving more sports and functional brain imaging techniques, as well as accurate measurements of head impacts, can add to our understanding of longitudinal mechanisms of subconcussive and concussive head impacts in sports. The present findings suggest rCBF may reflect dynamic changes that could be indicative of long-term physiological consequences in high-contact sports.

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Author Contributions

M.M.Z., G.G., D.B.C., and M.K were responsible for the conception and design of the study. M.K., M.G., M.M.Z., B.D.M., M.Y.Z., D.T., H.M., M.W., G.G., and G.Z. were responsible for Acquisition and analysis of data. M.K., M.G., M.Y.Z., M.G., H.M., B.D.M, N.M., S.S., M.W., G.G., D.B.C., M.E.M., G.Z., and M.M.Z. were responsible for drafting the text or preparing the figures.

Potential Conflicts of Interest

Dr Zeineh receives research funding from General Electric Healthcare.

Data Availability Statement

All data associated with this study are available in the main text or the supplementary materials. All the imaging data can be shared upon request with a proposal and under a data transfer agreement.

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