

# Transcranial Photobiomodulation Promotes Neurological Resilience in Current Collegiate American Football Players Exposed to Repetitive Head Acceleration Events

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## Abstract

Repetitive head acceleration events (RHAЕ) are common in contact sports and associated with neuroinflammation, axonal injury, and long-term neurological impairments, including increased risk for chronic traumatic encephalopathy. Current strategies for addressing RHAЕ focus on post-injury care rather than proactive neuroprotection, leaving athletes vulnerable to cumulative neurotrauma. Transcranial photobiomodulation (PBM) has shown promise in reducing neuroinflammation and promoting neuroprotection in traumatic brain injury; however, its potential to mitigate the structural brain changes associated with RHAЕ in actively competing athletes has not been investigated. The aim of this study was to investigate whether PBM mitigates RHAЕ-related neuroinflammatory and microstructural changes in collegiate American football players over a single National Collegiate Athletic Association Division I season. We hypothesized that restricted diffusion imaging (RDI) and quantitative anisotropy (QA), diffusion magnetic resonance imaging markers of neuroinflammation and axonal remodeling, respectively, would increase in the Sham PBM group due to RHAЕ exposure but remain stable in the Active PBM group, indicating neurological resilience. Twenty-six collegiate football players were randomly assigned to Active ( $n = 13$ ) or Sham ( $n = 13$ ) PBM groups. PBM (810 nm) was self-administered 3 days a week under supervision in the athletic training room with a transcranial plus intranasal device throughout the preseason practice period and regular season (16 weeks). Diffusion MRI data were collected pre- and postseason, and correlational tractography was used to assess the effects of PBM on longitudinal changes in RDI and QA. Moderation analyses examined time  $\times$  group interactions, with post hoc analyses exploring within- and between-group differences in RDI and QA cross-sectionally and longitudinally. Correlational tractography revealed significant main effects and interactions of time and group, with widespread increases in RDI and QA observed in the Sham PBM group over the season, consistent with neuroinflammation and axonal remodeling. In contrast, the Active PBM group showed relative stability in RDI and QA over time, with significant reductions observed in some areas. These findings suggest that PBM may mitigate ongoing neuroinflammation and facilitate the recovery processes. This study provides the first evidence suggesting that transcranial PBM reduces neuroinflammatory and axonal injury markers in American collegiate football players over a single season. PBM may serve as a noninvasive and accessible intervention for mitigating the cumulative neurological effects of RHAЕ exposure, offering a neuroprotective strategy for athletes participating in collision and contact sports. Future research should

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examine the long-term benefits of PBM across multiple seasons and its impact on functional outcomes to further establish the role of PBM in athlete brain health and wellness.

**Keywords:** connectometry; diffusion weighted imaging; neuroinflammation; photobiomodulation; repetitive head impacts; sport-related concussion

## Introduction

Public awareness of the cumulative effects of repetitive head acceleration event (RHAE) exposure has increased over the past decade, driving advancements in injury identification, diagnosis, and management.<sup>1</sup> However, despite growing recognition of the long-term risks associated with RHAE, effective treatment or prevention strategies remain limited.<sup>2</sup> RHAE refers to any external, short-duration collision force that accelerates the head either directly when applied to the skull or indirectly through forces applied to the body. Unlike repetitive head impacts (RHI), which involve direct head contact, RHAE encompasses a broader range of events common in contact sports that may not cause immediate or overt symptoms. The expanded classification recognizes that cumulative exposure to indirect forces may potentially affect brain health over time.<sup>3,4</sup> Relative to sport-related concussion (SRC),<sup>5</sup> the chronic effects of RHAE are less understood. Estimates from accelerometer measurements suggest that—based on SRC rates of  $\sim 0.1$  to  $0.6$  per player per season<sup>6–8</sup>—between 125 and 440 head acceleration events occur for every one SRC in collegiate and professional football players, with individual players experiencing up to 77 head acceleration events in a single season.<sup>9,10</sup> Accumulating evidence suggests that exposure over a single football season is associated with poorer cognitive performance,<sup>11</sup> abnormal brain activation patterns,<sup>12,13</sup> decreased white matter integrity,<sup>14</sup> and increased neuroinflammatory biomarkers<sup>15</sup> in the absence of immediate or overt symptoms. These findings suggest that cumulative RHAE exposure may contribute to long-term neurological impairments and traumatic encephalopathy syndrome (TES),<sup>16</sup> even in the absence of diagnosed concussion. The potential long-term effects of RHAE parallel those of SRC, with both increasing the risk of neurodegenerative disease,<sup>17–21</sup> yet only RHAE exposure is necessary for the development of TES and chronic traumatic encephalopathy (CTE).<sup>16,22,23</sup> Given these risks, identifying effective methods to mitigate the long-term consequences of RHAE is necessary to ensure the safety and longevity of collision and contact sports.

Emerging evidence in animal and human studies suggests that neuroinflammation secondary to RHAE drives long-term neurological deficits. In the absence of overt tissue damage, acute inflammation triggers the release of cytokines and chemokines that activate an intrinsic repair response,<sup>24,25</sup> providing active neuroprotective signals

and promoting axonal recovery and growth.<sup>26,27</sup> However, chronic, unregulated inflammation is marked by a sustained elevation of cytokine levels, increased oxidative stress, and the release of various inflammatory mediators. This persistent inflammatory response leads to ongoing microglial and astrocyte activation, which can damage neurons, disrupt synaptic signaling, and impair neuroplasticity.<sup>28,29</sup> Over time, these processes contribute to the downregulation of reparative mechanisms, neuronal loss, and ultimately drive long-term neurological deficits such as cognitive decline and mood disorders.<sup>30</sup> Furthermore, subsequent trauma exacerbates active inflammation, leading to an exaggerated pro-inflammatory response, progressive neurodegenerative pathology, and cumulative functional deficits.<sup>31–33</sup> To evaluate treatments that target these underlying injury mechanisms and reduce the risk of progressive neurodegenerative disease, it is essential that sensitive biomarkers are used to quantify the extent of neuroinflammation resulting from RHAE exposure.

Microstructural and inflammatory alterations resulting from RHAE are typically examined using scalar, tensor-derived metrics, such as fractional anisotropy and mean diffusivity, but findings from previous studies are inconsistent.<sup>34–36</sup> This variability is likely due to inherent limitations of the diffusion tensor model,<sup>37–40</sup> such as its inability to distinguish between restricted and nonrestricted diffusion within a voxel—a critical factor in assessing tissue microstructure, particularly in the presence of inflammation. Consequently, changes in tensor-derived metrics reflect a mix of biological processes, including edema, inflammation, and crossing fibers, making them less precise and reliable, especially in studies with smaller sample sizes. Advanced diffusion magnetic resonance imaging (MRI) approaches, such as generalized  $q$ -sampling imaging (GQI),<sup>41</sup> offer improved sensitivity over traditional tensor-based methods by separating restricted from nonrestricted diffusion and providing fiber-specific measures of white matter integrity. Two key GQI-derived metrics are quantitative anisotropy (QA), an index of axonal organization, plasticity, and repair,<sup>42</sup> and restricted diffusion imaging (RDI), which reflects immune cell-related changes in tissue density and serves as a sensitive marker of neuroinflammation.<sup>43</sup> As neuroinflammation is increasingly recognized as a key contributor to long-term neurological impairment in contact sports, RDI holds significant potential as a biomarker for monitoring the effects of

RHAЕ, enabling earlier detection of neuroinflammatory changes compared with traditional diffusion metrics.

Current strategies for addressing RHAЕ primarily focus on post-injury care, including rest, symptom management, and exercise.<sup>44,45</sup> While helmet improvements and rule changes aim to reduce head injuries, they neither prevent nor treat the cumulative effects of RHAЕ exposure. Cognitive rehabilitation and most pharmacological treatments offer potential benefits but are reactive rather than preventative, resource-intensive, and impractical for widespread use in athletes.<sup>44,45</sup> This highlights the need for a noninvasive, cost-effective intervention that can enhance neurological resilience to the effects of RHAЕ exposure before symptoms appear. Photobiomodulation (PBM) is a noninvasive, easy-to-use, and well-tolerated intervention with broad therapeutic applications,<sup>46–48</sup> including sports injury rehabilitation,<sup>49–51</sup> and has demonstrated several biological benefits that are important in the context of brain injury.<sup>52–54</sup> When applied to the head, PBM delivers red to near-infrared (NIR) light through light-emitting diodes (LEDs) or lasers to targeted brain regions, activating mitochondrial responses that enhance adenosine triphosphate production<sup>55</sup> and promote healthy circulation, thereby facilitating nutrient and oxygen delivery to the damaged tissues.<sup>56–58</sup> PBM can modulate the activity of inflammatory mediators, such as cytokines, prostaglandins, and nitric oxide, effectively reducing inflammation, promoting tissue repair, and preventing secondary damage caused by excessive immune responses.<sup>59–61</sup> In addition, PBM can mitigate other key pathophysiological effects of brain injury, including axonal injury, oxidative stress, excitotoxicity, and apoptosis.<sup>52–54,62,63</sup> The cellular mechanisms of PBM regulate calcium and reactive oxygen species levels and promote axonal repair and regeneration, thereby addressing chronic postconcussion symptoms and preserving cellular homeostasis.<sup>62,64–67</sup> Ultimately, PBM not only treats existing tissue damage but may also confer protective effects that enhance resilience against future insults.<sup>54,57</sup> Leveraging this resilience-building capability during active exposure periods could significantly mitigate the long-term neurological impairments linked to RHAЕ. This study explicitly evaluates whether PBM administered throughout a single collegiate football season preserves white matter integrity by reducing or preventing the deleterious brain alterations typically observed following RHAЕ exposure.

In animal TBI models, PBM is consistently associated with improvements in cognitive and motor function, reductions in lesion size and inflammation, improved recovery, and protection against secondary brain damage.<sup>59,68–73</sup> Recent human studies have demonstrated improvements in attention, processing speed, sleep quality, and reductions in

headaches and depression and anxiety symptoms.<sup>74–79</sup> Neuroimaging findings indicate that PBM enhances cerebral blood flow,<sup>80</sup> functional connectivity,<sup>81,82</sup> structural recovery,<sup>83</sup> and white matter organization,<sup>84</sup> suggesting neurological recovery in key brain networks. A limited number of case studies have explored the potential of PBM in humans with RHAЕ exposure,<sup>80,85</sup> and their findings similarly provide support for PBM as an effective treatment for the long-term consequences of cumulative RHAЕ. Furthermore, our recent work assessing the effects of PBM on neuromuscular control<sup>86</sup> and cognition<sup>79</sup> in individuals with a history of RHAЕ exposure demonstrated significant improvements in reaction time, grip strength, postural control, memory, executive functioning, attention, processing speed, and fluid intelligence following 8–10 weeks of PBM treatment. Given these findings, along with the consistent benefits of PBM reported in the traumatic brain injury (TBI) literature and its well-documented effects on inflammation, axonal repair, and neuroprotection, it follows that PBM could enhance neurological resilience to RHAЕ exposure in athletes currently participating in contact sports, including American football; however, there are currently no published investigations of the effects of PBM on the microstructural integrity of the brain in this population.

The cumulative effects of RHAЕ and the potential protective mechanisms of PBM are expected to manifest as subtle and spatially heterogeneous changes within white matter. For this reason, an analytic method capable of detecting subtle, localized alterations in white matter organization is necessary. Diffusion studies have traditionally relied on tract-average diffusion estimates, which can obscure region-specific changes and diminish the sensitivity of the findings. Diffusion connectometry overcomes these limitations by quantifying the degree of connectivity between adjacent voxels within the white matter.<sup>87</sup> Connectometry can be used to perform correlational tractography, which utilizes permutation testing to identify specific tract segments that are significantly associated with a study-related variable of interest. Unlike tract-averaged or streamline-based approaches, correlational tractography is not constrained to predefined regions and can detect focal microstructural changes related to inflammation or axonal repair that might otherwise be obscured. This makes it particularly well suited for evaluating whether PBM confers resilience to the diffuse and variable white matter changes associated with RHAЕ. Furthermore, a recent feasibility study demonstrated the success of correlational tractography in monitoring disease progression in mild TBI, where QA was shown to be a potential biomarker of white matter injury and/or repair.<sup>88</sup>

The present study utilizes correlational tractography to assess the relationship between pre- to postseason

changes in diffusion markers of neuroinflammation and axonal damage in American collegiate football players who received active PBM treatment relative to those who received sham PBM treatment. Based on the known mechanisms of PBM and the expectation that the athletes will be exposed to RHAE throughout a season of play, we hypothesized that RDI and QA will increase across the season in the Sham PBM group, indicating neuroinflammation and the associated initiation of axonal repair mechanisms, whereas RDI and QA will remain relatively stable in the Active PBM group, indicating neurological resilience to the effects of RHAE.

## Materials and Methods

### Participants

We initially recruited 40 members from a National Collegiate Athletic Association (NCAA) Division I American football team at a university in the Western United States using a double-blind intervention procedure, with participants randomly assigned to Active ( $n = 20$ ) or Sham ( $n = 20$ ) PBM groups. All procedures were approved by the local Institutional Review Board, and participants provided written informed consent. All study procedures were performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments. Eligibility criteria included active enrollment on the local NCAA Division I American football roster, age  $\geq 18$  years, and English proficiency. Exclusion criteria included contraindication to MRI. Recruitment involved an initial presentation by a certified athletic trainer, flyers, and messages from athletic training staff, with no coach involvement, ensuring confidentiality and nondisclosure to coaching staff. To maintain participant confidentiality, player position is not reported; however, players are categorized according to RHAE exposure profiles, based on the definitions provided by Kartou et al.<sup>89</sup> Accordingly, players who are exposed to more frequent, lower magnitude impacts, including offensive and defensive linemen, were categorized into a “high frequency/low strain” exposure profile; quarterbacks, wide receivers, and defensive backfield players who are exposed to less frequent but higher magnitude impacts were categorized into a “low frequency/high strain” exposure profile; and players who are exposed to impacts of moderate magnitude at a moderate frequency, including linebackers, running backs, and tight ends, were categorized into a “moderate frequency/strain” exposure profile. A pseudorandom assignment method, using a random number generator, was used to balance group sizes. Participants received a \$250 gift card as compensation.

### Intervention

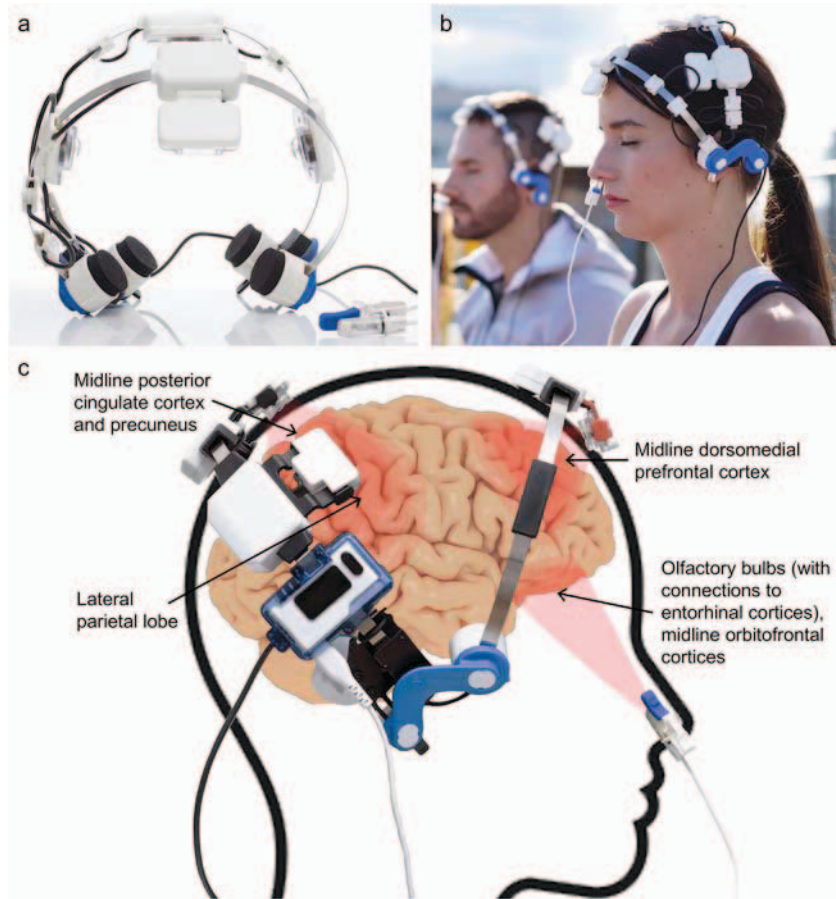
Participants received an active or sham Vielight (Toronto, Ontario, Canada) Neuro Gamma (v3) transcranial plus intranasal PBM device (Fig. 1) at the start of

the preseason practice period (fall camp) and were instructed on its proper use and maintenance. Treatments were self-administered under supervision of research staff in the athletic training room or in a designated, private space when traveling to away games. The sham and active PBM devices are identical, but no NIR light is delivered by the sham device once it is placed upon the head. The headsets include four NIR LEDs targeting cortical nodes of the default mode network:<sup>90</sup> the midline dorsomedial prefrontal cortex, the right and left lateral parietal lobes, and the midline posterior cingulate cortex and precuneus. In addition, an intranasal LED is positioned over capillaries in the nasal epithelium, targeting the olfactory bulbs, midline orbitofrontal cortex, and entorhinal cortices (indirectly through olfactory bulbs).<sup>85</sup> Additional details with device specifications are provided in Table 1. The treatment protocol was developed in accordance with device manufacturer recommendations and consisted of single 20-min treatment sessions, administered three times per week throughout the 16-week NCAA Division 1 fall camp and regular season.

### Neuroimaging procedure

**Acquisition.** All MRI data were acquired on a 3 Tesla Siemens Tim Trio full-body scanner with a 32-channel head coil. Diffusion data were acquired using a multi-shell high-angular resolution diffusion imaging scheme, where 16  $b_0$  volumes were collected and 64 diffusion directions were sampled across each of three shells with  $b$ -values of 500, 1,000, and 2,000  $\text{s/mm}^2$  in both anterior-to-posterior (AP) and posterior-to-anterior (PA) phase encoding directions. Additional acquisition parameters were the following: TR/TE = 3,300/112 ms, voxel size = 2.4 mm isotropic, field of view (FOV) = 96 mm, and flip angle =  $90^\circ$ .

**Preprocessing.** The diffusion data were first denoised and then corrected for Gibbs ringing artifacts using MRtrix<sup>91</sup> 3.0 `dwidenoise` and `mrdegibbs` tools, respectively. The first  $b_0$  was then extracted from each of the AP and PA datasets, and the PA  $b_0$  was nonlinearly registered to the AP  $b_0$  using ANTs (`antsRegistrationSyNQuick.sh`).<sup>92,93</sup> The resulting distortion field was used to transform the denoised/degibbsed PA image to match the denoised/degibbsed AP image, and these final AP and PA images were concatenated into a single diffusion-weighted imaging dataset. The FMRIB Software Library (FSL)<sup>94</sup> 6.0.5 `topup` tool was applied to the first  $b_0$  images extracted from the AP and PA datasets in the previous step to estimate the susceptibility-induced off-resonance field. A temporary brain mask was also created using a mean-corrected  $b_0$  image that was generated from the output of `topup`. Finally, the temporary mask and distortion field from `topup` and the single diffusion-weighted imaging dataset (AP+PA)



**FIG. 1.** Transcranial plus intranasal photobiomodulation (PBM) device. The PBM device used in the present study is shown in the top left panel (a) along with an example of how it is placed properly upon the head (b). The brain regions targeted by each light-emitting diode (LED) are depicted in the bottom panel (c).

created previously were fed into the FSL eddy tool to correct for eddy currents, motion, and susceptibility-induced distortions.

**Quality control.** The following quality control protocol<sup>95</sup> was applied to the preprocessed data to minimize the likelihood of false positive results: (1) confirmation of image acquisition (i.e., image dimension, resolution, and *b*-table) consistency between pre- and postseason scans (one dataset was excluded based on this criterion); (2) calculation of the neighboring diffusion-weighted correlation coefficient<sup>95</sup> and exclusion of data with between-subject scan differences of  $r \geq 0.1$  (one dataset was excluded based on this criterion); (3) assessment of signal dropout for each slice of each diffusion image, with a threshold for inclusion of  $< 1\%$  of slices affected<sup>95</sup> (one dataset was excluded based on this criterion); (4) confirmation of correct *b*-table orientation using the fiber coherence index.<sup>96</sup>

Reconstruction. The spin distribution function was obtained for each participant and at each time point by reconstructing the diffusion data in Montreal Neurological Institute (MNI) space using *q*-space diffeomorphic reconstruction<sup>97</sup> with a diffusion sampling length ratio of 1.25 and an isotropic 2 mm output resolution. From the spin distribution function, normalized QA was derived as a measure of anisotropic diffusion density along the peak fiber orientation. QA provides fiber-specific estimates within each voxel, offering improved accuracy over fractional anisotropy in regions with crossing fibers and in low signal-to-noise environments, and is less affected by confounding factors such as edema, inflammation, and partial volume effects.<sup>41,42,98</sup> Higher QA is generally associated with greater axonal integrity and plasticity, but it also increases alongside cognitive impairment in the acute stages of mild TBI.<sup>88</sup> This may reflect enhanced extracellular water transfer due to axonal stretching and deformation or in the presence of tissue expansion from

**Table 1. Transcranial Plus Intranasal Photobiomodulation Device Specifications and Settings**

<i>Specifications</i>				
Manufacturer	Vielight, Inc. (Toronto, Ontario, Canada)			
Model	Neuro Gamma v3 (2020)			
Number of emitters	5			
Emitter type	Light emitting diode (LED)			
Center wavelength	810 nm			
Spectral bandwidth	Full width half max: $\pm 20.2$ nm			
Operating mode	Pulsed			
Frequency	40 Hz			
Duty cycle	50%			
Pulse on duration	25 ms			
Aperture diameter	1 cm <sup>2</sup>			
Beam shape	Circular			
Beam divergence	0 degrees on contact			
Exposure duration	1,200 sec * 0.5 (duty cycle) = 600 sec			
Total intervention exposure	3 days per week over 16 weeks (max 48 sessions)			
<i>Emitter distribution, irradiance, and energy delivered</i>				
<i>Energy source</i>	<i>Nasal applicator</i>	<i>Headset</i>		
		<i>Anterior</i>	<i>Lateral</i>	<i>Posterior</i>
LEDs	1	1	2	1
Beam spot (cm <sup>2</sup> )	1	1	1	1
Wavelength (nm)	810	810	810	810
Pulse rate (Hz, 50% duty-cycle)	40	40	40	40
Power output density (mW/cm <sup>2</sup> )	25	75	100	100
Energy dose density (J/cm <sup>2</sup> )	15	45	60	60
Tissue penetrated	Mucosa	Scalp	Scalp	Scalp
Target(s)	Midline orbitofrontal cortex, bilateral olfactory bulbs with connections to entorhinal cortices	Midline dorsomedial prefrontal cortex	Left and right lateral parietal lobes	Midline precuneus, posterior cingulate cortex
Total energy deposition				
Per session		15 J/cm <sup>2</sup> + (3 * 60 J/cm <sup>2</sup> ) + 45 J/cm <sup>2</sup> = 240 J/cm <sup>2</sup>		
Total intervention (maximum)		240 J/cm <sup>2</sup> * 48 sessions = 11,520 J/cm <sup>2</sup>		

cytotoxic edema, resulting in an increase in diffusion density along the affected tracts. RDI, a nonparametric GQI-derived tensor algorithm, was additionally calculated. RDI isolates restricted diffusion within a voxel and exhibits a strong correlation ( $r > 0.99$ ) with cell density due to immune cell infiltration.<sup>43</sup> In contrast to mean diffusivity, which is confounded by coexisting cytotoxic and vasogenic edema, RDI's ability to effectively differentiate between restricted and nonrestricted diffusion provides it with superior sensitivity and specificity in detecting inflammation-related changes in brain tissue.<sup>43,99</sup>

All data that passed the quality control checks were reconstructed and subjected to visual inspection of data quality, which resulted in the exclusion of one additional dataset due to poor  $q$ -space diffeomorphic reconstruction quality. The remaining data were compiled into a single longitudinal connectometry database for each metric. Longitudinal change was calculated as the absolute difference (postseason–preseason), and no filter was applied for the directionality of results.

Connectometry. Diffusion MRI connectometry<sup>87</sup> was performed in DSI Studio (“Hou” January 30, 2025 GPU build for PC),<sup>100</sup> from which correlational tractography

was used to investigate the effect of PBM treatment on RDI and QA throughout the football season. For each metric, a moderation analysis was performed to assess the effects of time (0, preseason; 1, postseason), group (0, Sham PBM; 1, Active PBM), and the interaction of time  $\times$  group. Given significant main and/or interaction effects, the following post hoc correlational tractography analyses were also performed: (1) cross-sectional differences in RDI/QA between groups at each time point, (2) longitudinal changes in RDI/QA within each group, and (3) longitudinal changes in RDI/QA between groups.

For all analyses, partial Spearman correlations were performed on the local connectomes, controlling for presence or absence of previous TBI(s) and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared [kg/m<sup>2</sup>]) at the respective time point (cross-sectional) or change in BMI (longitudinal), given their associations with axonal injury and inflammation.<sup>101,102</sup> In addition, a moderation analysis tests each effect (e.g., time  $\times$  group) while controlling for the other two effects (e.g., time, group); thus, each moderation analysis includes four covariates. Due to the small sample size and concern for overfitting the models, the moderations were performed a second time, without

controlling for the effects of TBI history and BMI, and these results are provided in the Supplementary Data for comparison.

For all correlational tractography analyses, fiber tractography was performed on all tracts exceeding a T-statistic threshold of 3.5 using a deterministic fiber tracking algorithm,<sup>42</sup> and a length threshold of 20 voxels (40 mm) was used to identify associated tracts. Sixteen iterations of topology-informed pruning were applied to remove false tracts.<sup>103</sup> To estimate the false discovery rate (FDR), a total of 10,000 randomized permutations, each with 128,000 whole brain seeds, were applied to the group label to obtain the null distribution of the track length, and significant results were limited to those with  $FDR \leq 0.05$  at the minimum tract length.<sup>95</sup> To account for cases where the inferior cerebellar region was excluded from the FOV, a region of avoidance was applied to exclude the cerebellum at the level of Crus II and below, ensuring that tractography was restricted to areas outside this region.

### Statistical analysis

Demographic variables were assessed for normality and homogeneity of variance using Shapiro–Wilks and Levine’s tests, respectively, as appropriate. BMI was missing for two participants at the postseason assessment, and these data were imputed using multiple imputation with predictive mean matching ( $knn = 3$ ). Independent samples *t*-tests and Kruskal–Wallis tests were used to assess between-group differences in continuous demographic variables that met and violated parametric assumptions, respectively. All categorical demographic variables were assessed for group differences using Pearson’s chi-square tests of independence.

## Results

### Participants

Of the 40 participants recruited, three declined to participate, two were lost to follow-up, four were missing post-season diffusion data, four datasets did not pass quality control checks (see details above), and one was excluded due to an incidental finding on imaging. The final sample included in the present analysis consisted of 26 male athletes between the ages of 18 and 25 years ( $M = 21.82 \pm 1.78$ ) with 12–16 years of education ( $M = 14.15 \pm 1.41$ ). Group-level sample characteristics are reported in Table 2. No significant group differences were observed across demographic, injury, or treatment characteristics, with the exception of preseason BMI ( $p = 0.037$ ), which was higher in the Active PBM group ( $M = 31.02 \pm 4.44$ ), relative to the Sham PBM group ( $M = 27.62 \pm 3.30$ ). Participants began treatment during the first week of fall camp (Mdn = 4, IQR = 4 to 5 days after first day of practice) and completed treatment the final week of the

regular season (Mdn = 2, IQR = 2 to 3 days before the last regular game).

### Correlational tractography

**Moderation analysis.** Correlational tractography was used to determine if group assignment moderated the relationship between time and RDI (Fig. 2a, Table 3), with the effects of TBI history and BMI removed. The results demonstrated a significant main effect of time on RDI, where RDI was significantly increased at postseason across groups, relative to preseason ( $T = 1.97$ ,  $FDR = 0.000$ ). A significant main effect of group on RDI was also observed, where RDI was significantly higher in the Sham PBM group across time, relative to the Active PBM group ( $T = 1.94$ ,  $FDR = 0.000$ ). A significant time  $\times$  group interaction was also observed, such that RDI was significantly decreased over time in the Active PBM group, relative to the change in RDI over time in the Sham PBM group ( $T = 0.97$ ,  $FDR = 0.021$ ).

Correlational tractography was also used to determine if group assignment moderated the relationship between time and QA (Fig. 2b, Table 3), and a significant main effect of time on QA was observed, such that QA was significantly increased at postseason across groups, relative to preseason ( $T = 1.89$ ,  $FDR = 0.000$ ). A significant main effect of group was also observed, such that QA was significantly higher in the Sham PBM group across time, relative to the Active PBM group ( $T = 2.12$ ,  $FDR = 0.000$ ). Finally, a significant time  $\times$  group interaction was observed, such that QA was significantly reduced over time in the Active PBM group, relative to the change in QA over time in the Sham PBM group ( $T = 0.91$ ,  $FDR = 0.003$ ).

The supplemental moderation analyses, where BMI and TBI were not included as covariates, produced very similar results to those reported above for both RDI and QA (Supplementary Table S1 and Supplementary Fig. S1), but with slightly smaller effect sizes. However, the interaction of time  $\times$  group on QA affects a larger portion of the white matter (forceps major, forceps minor, left corticospinal tract, left arcuate fasciculus, left cerebellum), likely due to the increased statistical power in these supplemental analyses.

**Cross-sectional differences between groups.** Given the significant main effect of group assignment on both RDI and QA across time, post hoc correlational tractography analyses were performed to explore group differences in these metrics at each time point (Fig. 3, Table 3). Significant differences in RDI were observed between groups at preseason, where higher RDI was observed throughout the brain in the Sham PBM group, relative to the Active PBM group ( $T = 1.48$ ,  $FDR =$

**Table 2. Demographic, Injury, and Treatment Characteristics of the Present Sample**

Characteristic	Sham PBM (n = 13)		Active PBM (n = 13)		$\chi^2$	df	p
	n	%	n	%			
Current education level					3.02	3	0.405
Freshman	3	23.08	2	15.38			
Sophomore	1	7.69	1	7.69			
Junior	2	15.38	6	46.15			
Senior	7	53.85	4	30.77			
Dominant hand					1.18	1	0.593
Right	10	76.92	12	92.31			
Left	3	23.08	1	7.69			
Racial group					3.03	3	0.530
White/Caucasian	5	38.46	8	61.54			
Black/African American	2	15.38	3	23.08			
Pacific islander	2	15.38	1	7.69			
Mixed race	4	30.77	1	7.69			
Player position					2.26	3	0.683
Defensive line	4	30.77	2	15.38			
Defensive back	6	46.15	5	38.46			
Offensive line	0	0.00	1	7.69			
Offensive back	3	23.08	5	38.46			
Exposure profile					1.46	2	0.608
Low frequency, high strain	5	38.46	3	23.08			
Moderate frequency/strain	4	30.77	7	53.85			
High frequency, low strain	4	30.77	3	23.08			
History of previous TBI(s)					0.00	1	1.000
False	6	46.15	6	46.15			
True	7	53.85	7	53.85			
TBI sustained during treatment					0.38	1	1.000
False	11	84.62	12	92.31			
True	2	15.38	1	7.69			
	<i>M/Mdn</i>	<i>SD/IQR</i>	<i>M/Mdn</i>	<i>SD/IQR</i>	<i>t/χ<sup>2</sup></i>	<i>df</i>	<i>p</i>
Age (years)	21.92	2.22	21.77	1.36	0.21	24	0.833
Education (years) <sup>a</sup>	14.38	1.66	14.00	1.15	0.69	23	0.500
Number of previous TBIs	0.85	0.99	1.38	1.50	-1.08	24	0.291
Years since last TBI	6.71	2.69	3.57	3.26	1.97	12	0.073
Preseason BMI <sup>b</sup>	26.70	4.00	29.90	1.70	4.75		0.029
Postseason BMI <sup>b</sup>	26.60	4.00	29.00	4.20	2.95		0.086
BMI change over season	0.05	0.83	-0.52	0.94	1.66	24	0.110
Pre- to postseason MRI (days)	136.46	15.08	140.00	15.43	-0.59	24	0.560
Preseason MRI to first treatment (days)	16.85	16.39	19.08	13.65	-0.38	24	0.709
Last treatment to postseason MRI (days) <sup>b</sup>	11.00	23.00	23.00	19.00	0.13		0.718
Fall camp start to first treatment (days) <sup>b</sup>	4.00	2.00	4.00	0.00	0.48		0.489
Last treatment to final game (days) <sup>b</sup>	3.00	1.00	2.00	1.00	0.16		0.694
PBM sessions completed <sup>b</sup>	41.00	7.00	40.00	6.00	0.26		0.607
Treatment duration (weeks) <sup>b</sup>	16.00	0.00	16.00	0.00	0.13		0.716

Exposure profile refers to three position-specific profiles defined by Karton et al.<sup>89</sup> based on frequency of impact, tissue strain magnitude, and time interval between impacts, where low frequency/high strain consists of quarterbacks, wide receivers, and defensive backfield players; moderate frequency/strain includes linebackers, running backs, and tight ends; and high frequency/low strain includes offensive and defensive linemen.

Exact *p*-values are reported for chi-squared tests on categorical variables.

<sup>a</sup>Welch's *t*-test was used due to violation of homogeneity of variance.

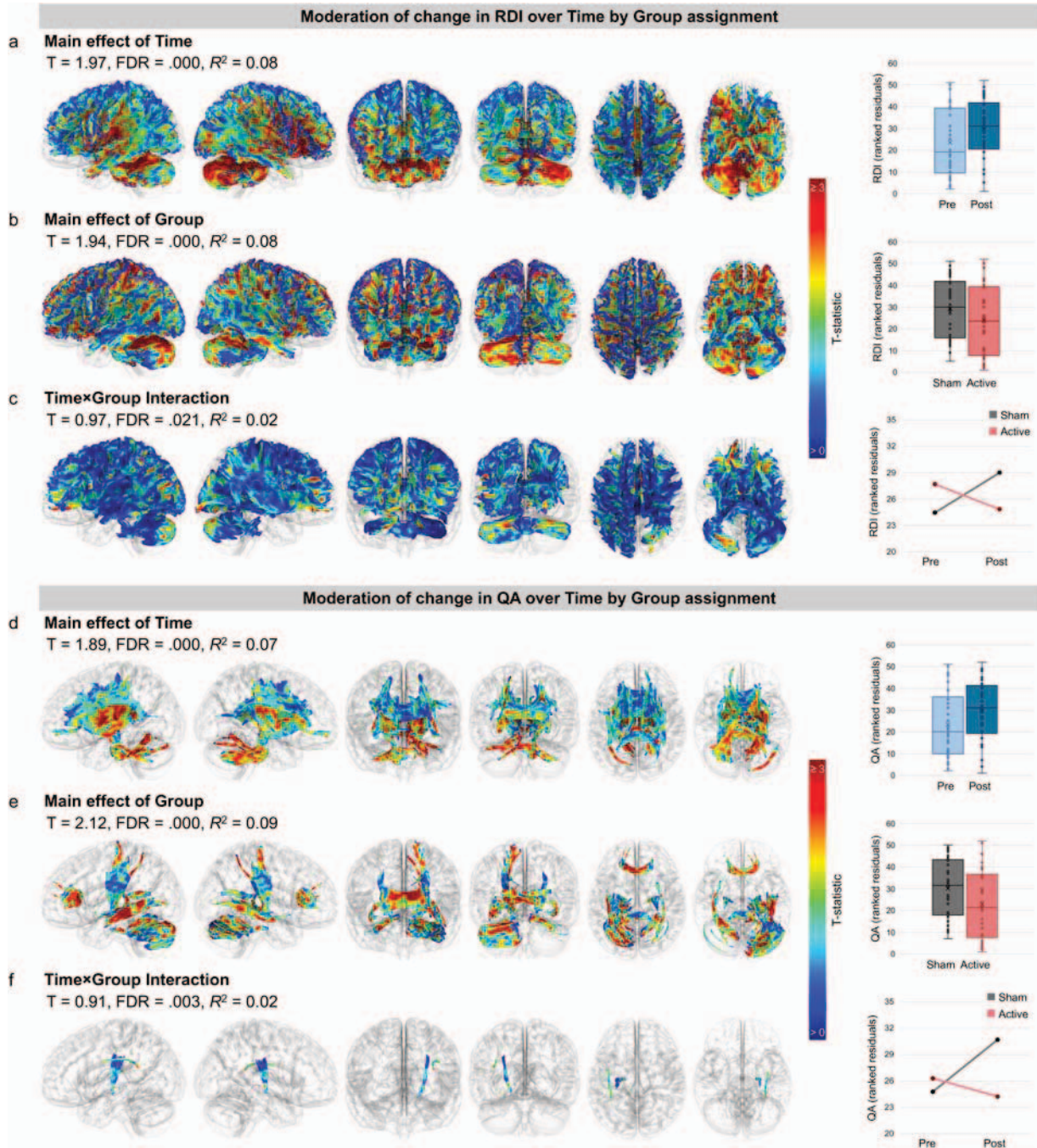
<sup>b</sup>Kruskal-Wallis test was used due to violation of normality.

PBM, photobiomodulation; TBI, diagnosed traumatic brain injury; BMI, body mass index; MRI, magnetic resonance imaging.

0.001). Significantly higher RDI was also observed throughout the brain in the Sham PBM group at postseason, but to a much larger extent than that which was observed at preseason ( $T = 2.16$ ,  $FDR = 0.000$ ).

Similarly, significantly higher preseason QA was observed in the Sham PBM group, relative to the Active PBM group ( $T = 1.54$ ,  $FDR = 0.000$ ), specifically in the left and right sagittal stratum, left optic radiation, forceps major and minor, body of the corpus callosum, left and right corticospinal tract, left medial lemniscus, thalamic

radiation, middle cerebellar peduncle, and left and right cerebellar lobes. Higher postseason QA was also observed in the Sham PBM group, relative to the Active PBM group, but with a larger effect size than that which was observed at preseason ( $T = 1.84$ ,  $FDR = 0.000$ ). In addition, at postseason, higher Sham PBM group QA was observed in the same tracts affected at preseason as well as the left corticostriatal tracts (including the medial forebrain bundle), fornix, cingulum, uncinate fasciculus, and extreme capsule.



**FIG. 2.** Correlational tractography results from moderation analyses. Resulting tract clusters are shown in glass surface renderings from sagittal, coronal, and axial views. The color of the tract reflects the strength of the relationship, where small, yet significant correlations are shown in dark blue, and large correlations appear in dark red. Box plots are provided to demonstrate the distribution of the main effects of time and group, and the interaction effects are demonstrated using line graphs. Ranked residuals of RDI and QA are charted after removing the effects of Group and Time × Group, Time and Time × Group, and Time and Group from the main effect of Time (**a, d**), main effect of Group (**b, e**), and the interaction of Time × Group (**c, f**), respectively; the effects of BMI and presence or absence of previous TBI were also removed from all analyses. Partial  $R^2$  values are provided to indicate the size of the overall effect, where  $R^2 \geq 0.01$ , 0.09, and 0.25 indicate small, moderate, and large effects, respectively. RDI, restricted diffusion imaging; QA, normalized quantitative anisotropy; BMI, body mass index; TBI, traumatic brain injury; PBM, photobiomodulation.

**Table 3. Detailed Results of Each Correlational Tractography Analysis**

Analysis	Description of change/difference	Streamlines	Volume (mm <sup>3</sup> )	M length (mm)	T	df	FDR	R <sup>2</sup>
RDI								
Moderation								
Time	Increased over Time, across Groups	2,001,610	674,810	63.30	1.97	46	0.000	0.08
Group	Higher in Sham PBM group, across Time	1,432,770	672,017	60.93	1.94	46	0.000	0.08
Time × Group	Lower in Active PBM group at postseason	192,551	379,791	56.96	0.97	46	0.021	0.02
Cross-sectional (between groups)								
Preseason	Higher in Sham PBM group at preseason	923,879	640,024	59.81	1.48	22	0.001	0.09
Postseason	Higher in Sham PBM group at postseason	1,833,890	689,130	59.79	2.16	22	0.000	0.18
Longitudinal								
Within Sham PBM	Increased over time within Sham PBM group	402,389	432,100	60.74	3.15	10	0.000	0.50
Within active PBM	Increased over time within active PBM group	275,541	448,324	72.49	0.97	10	0.064	0.09
	Decreased over time within active PBM group	227,128	308,440	56.90	0.77	10	0.015	0.06
Between groups	Greater Increase over time in Sham PBM group	993,708	646,841	61.44	1.32	22	0.000	0.07
QA								
Moderation								
Time	Increased over Time, across Groups	42,386	96,299	47.27	1.89	46	0.000	0.07
Group	Higher in Sham PBM group, across Time	16,708	53,787	46.73	2.12	46	0.000	0.09
Time × Group	Lower in active PBM group at postseason	77	1,478	43.13	0.91	46	0.003	0.02
Cross-sectional (between groups)								
Preseason	Higher in Sham PBM group at preseason	5,245	31,826	46.81	1.54	22	0.000	0.10
Postseason	Higher in Sham PBM group at postseason	17,149	54,192	47.67	1.84	22	0.000	0.13
Longitudinal								
Within Sham PBM	Increased over time within Sham PBM group	360,409	304,002	53.12	2.70	10	0.000	0.42
Within active PBM	Increased over time within active PBM group	21,827	75,745	49.60	0.91	10	0.000	0.08
	Decreased over time within active PBM group	28,733	60,652	53.88	0.76	10	0.000	0.05
Between groups	Greater Increase over time in Sham PBM group	61,410	142,157	53.28	1.48	22	0.000	0.09

10,000 permutations were used to calculate FDR of minimum tract length (40 mm). Partial  $R^2$  values are provided to indicate the size of the overall effect, where  $R^2 \geq 0.01$ , 0.09, and 0.25 indicate small, moderate, and large effects, respectively.

RDI, restricted diffusion imaging; PBM, photobiomodulation; QA, normalized quantitative anisotropy; FDR, false discovery rate.

**Longitudinal changes within groups.** Given the significant effect of time on both RDI and QA across groups, post hoc correlational tractography analyses were performed to explore changes in each metric over time within each group. In the Sham PBM group, significantly increased RDI was observed throughout the brain over time ( $T = 3.15$ ,  $FDR = 0.000$ ), while no tracts demonstrated reduced RDI (Fig. 4, Table 3). In the Active PBM group, increased RDI was observed in some tracts, but this result did not meet criteria for statistical significance ( $T = 0.97$ ,  $FDR = 0.064$ ; Supplementary Fig. S2). Other white matter areas, particularly in the left hemisphere, demonstrated significant reductions in RDI over time in the Active PBM group ( $T = 0.77$ ,  $FDR = 0.015$ ). A visualization of overlaying tracts with increased versus decreased RDI in the Active PBM group is provided in Supplementary Figure S3a.

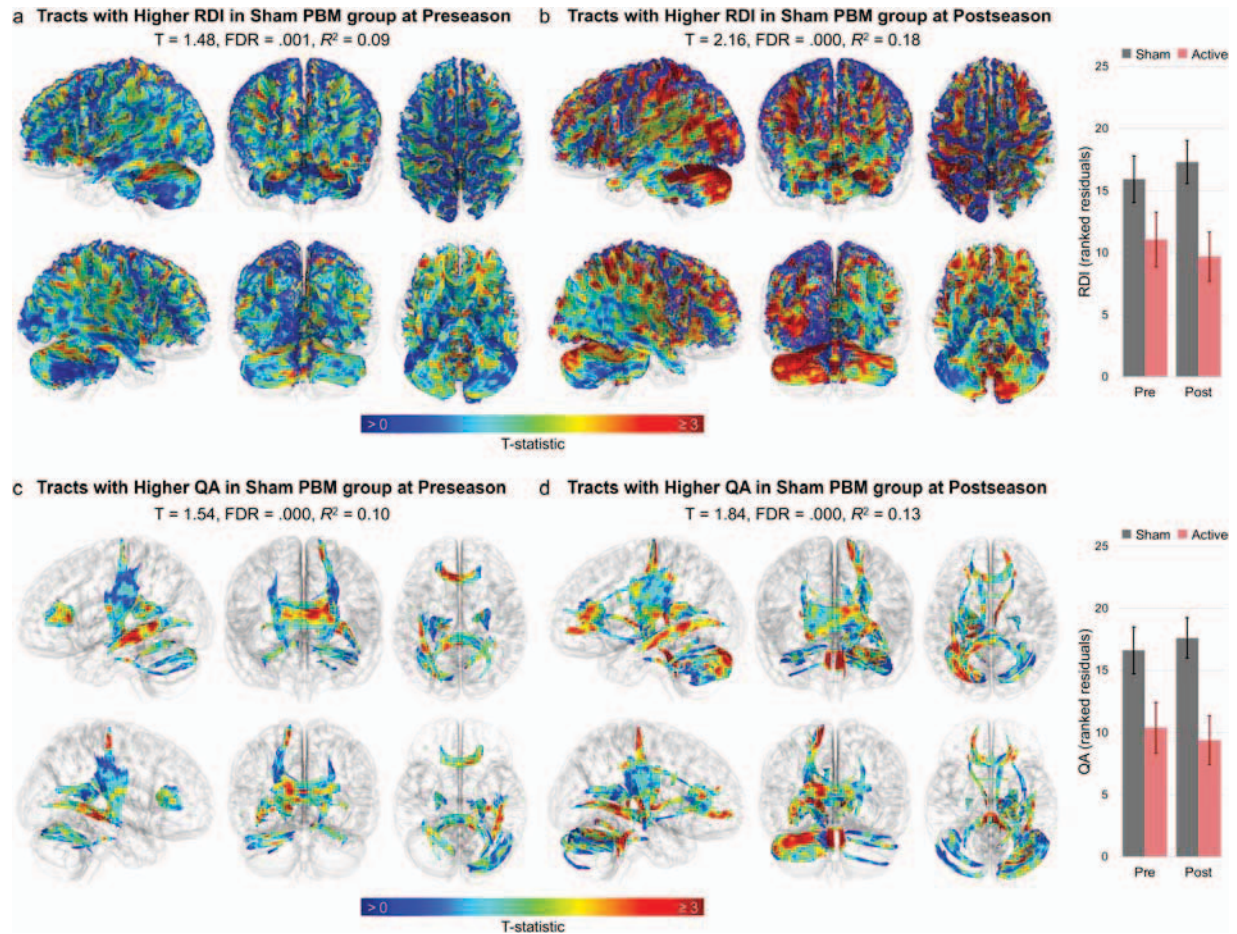
A similar pattern was observed with QA (Fig. 5, Table 3), where significantly increased QA was observed throughout the brain in the Sham PBM group over the course of the season ( $T = 2.70$ ,  $FDR = 0.000$ ), while decreased QA was not observed in any tracts. Significantly increased QA was observed in some deep white matter regions in the Active PBM group ( $T = 0.91$ ,  $FDR = 0.000$ ); however, the effect size was much smaller than that of the increase in QA seen in the Sham PBM group over time. Furthermore, several other tracts, particularly those of the posterior left hemisphere region,

demonstrated significant pre- to postseason decreases in QA ( $T = 0.76$ ,  $FDR = 0.000$ ) within the Active PBM group. A visualization of overlaying tracts with increased versus decreased QA in the Active PBM group is provided in Supplementary Figure S3b.

**Longitudinal changes between groups.** Given the significant time × group interaction effect on both RDI and QA, post hoc correlational tractography analyses were performed to explore between-group differences in change in RDI and QA over time (Fig. 6, Table 3). Correlational tractography demonstrated a significant relationship between pre- to postseason change in RDI and group assignment, where significantly increased RDI was observed throughout the brain in the Sham PBM group over time, relative to the Active PBM group ( $T = 1.32$ ,  $FDR = 0.000$ ). Similarly, a significant relationship between change in QA and group assignment was observed, where QA was significantly increased in the Sham PBM group over time, relative to the Active PBM group ( $T = 1.48$ ,  $FDR = 0.000$ ).

Video files displaying 360° rotation of results from each of the primary analyses, rendered with local T-statistic and directional color maps, can be accessed from <https://osf.io/94h8b/files/osfstorage>. Additional details are provided in Supplementary Table S3.

Due to the observed group differences in preseason RDI and QA, supplemental analyses were performed by

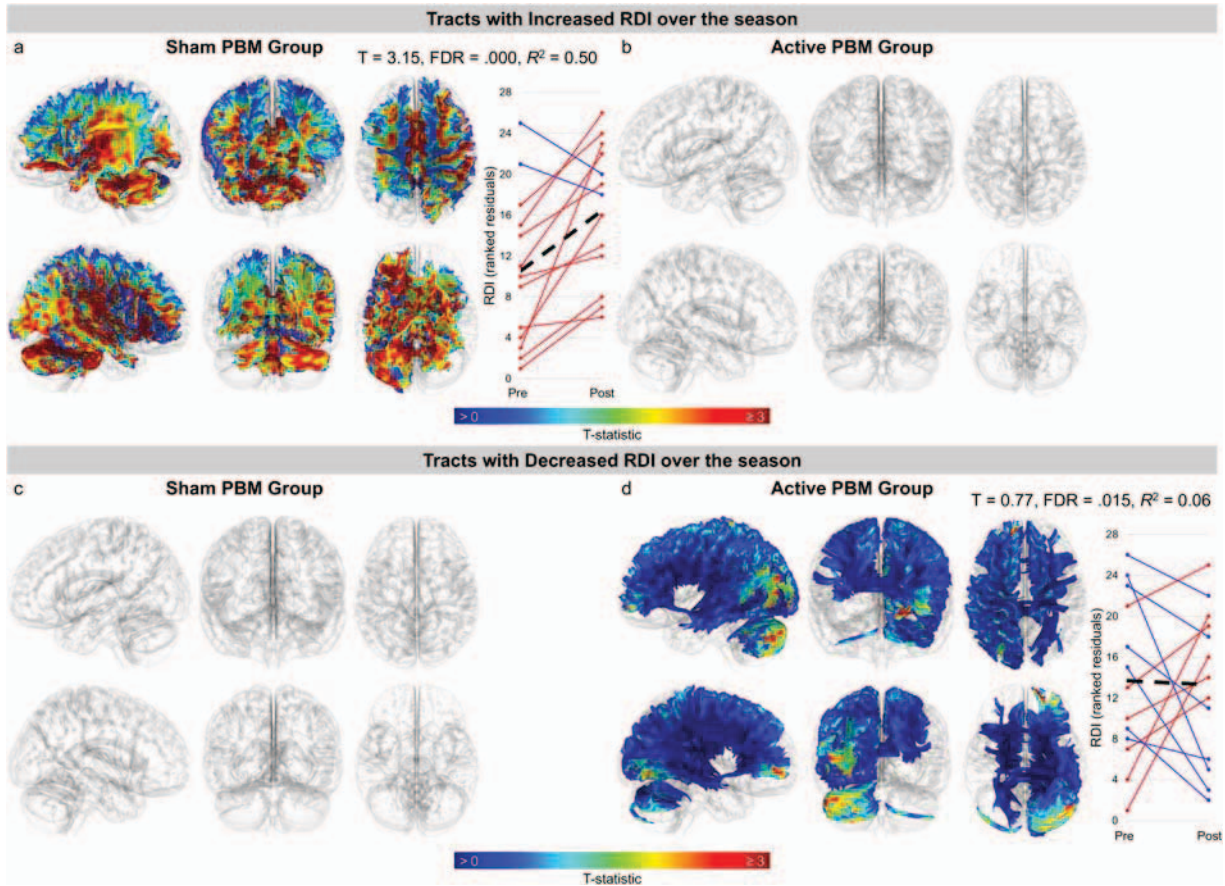


**FIG. 3.** Cross-sectional differences in RDI and QA between Sham and Active PBM groups. Correlational tractography revealed significantly higher RDI across tracts in the Sham PBM group, relative to the Active PBM group, at preseason (**a**) and postseason, but with a much larger effect (**b**). The Sham PBM group also had higher QA than the Active PBM group at preseason (**c**) and postseason, but also to a greater extent (**d**). Results are shown in glass surface renderings from lateral (left), coronal, and axial (right) views. The color of the tract reflects the strength of the relationship, where small yet significant correlations are shown in dark blue, and large correlations appear in dark red. Partial  $R^2$  values are provided to indicate the size of the overall effect, where  $R^2 \geq 0.01$ , 0.09, and 0.25 indicate small, moderate, and large effects, respectively. Bar graphs demonstrate statistically significant differences in mean ranked residual RDI and QA values (effects of BMI and previous TBI removed) between groups at each time point, and error bars reflect the standard error for each. RDI, restricted diffusion imaging; QA, normalized quantitative anisotropy; PBM, photobiomodulation; BMI, body mass index; TBI, traumatic brain injury; FDR, false discovery rate.

additionally controlling for preseason RDI and QA in each of the respective models. These results are presented in Supplementary Table S3 and Supplementary Figures S4, S5, S6, S7 and S8. A detailed discussion of the results is also provided in the Supplementary Data. Briefly, the inclusion of preseason RDI/QA did not alter the primary conclusions, suggesting that the observed effects of PBM are robust to preseason group differences in RDI and QA.

### Discussion

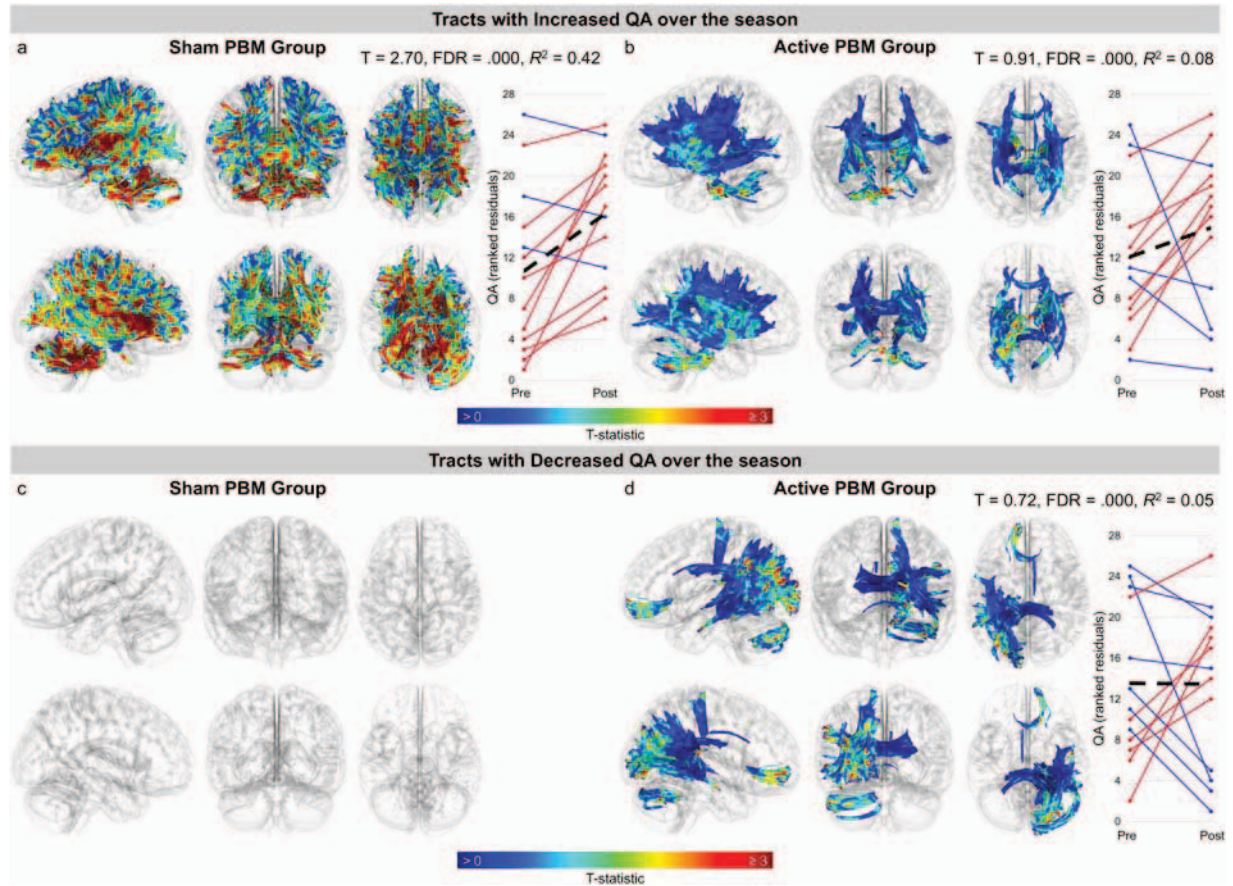
Our findings are the first to demonstrate that transcranial PBM mitigates the neuroinflammatory responses associated with RHAЕ exposure throughout a single collegiate football season. Using correlational tractography, we identified significant differences in pre- to postseason changes in neuroinflammatory and axonal injury markers between athletes who received active versus sham PBM treatment. Given the benefits of PBM for addressing the



**FIG. 4.** Longitudinal changes in RDI within each group. Tracts with significantly increased RDI from pre- to postseason in the Sham PBM group (**a**). No tracts were found with significantly increased RDI in the Active PBM group (**b**). In contrast, no tracts were found to have decreased RDI in the Sham PBM group (**c**), whereas significant decreases in RDI were observed across various tracts in the Active PBM group, particularly in the left hemisphere (**d**). Results are shown in glass surface renderings from sagittal, coronal, and axial planes. The top rows depict left, anterior, and superior views, and right, anterior, and inferior views appear in the bottom rows. The color of the tract reflects the strength of the relationship, where small yet significant correlations are shown in dark blue, and large correlations appear in dark red. Spaghetti plots of subject-specific changes in ranked residuals of RDI (effects of BMI and previous TBI removed) over time are provided for each significant within-group change in RDI observed, where increases are plotted in red and decreases in blue. The black dashed line overlaid on each plot represents the average pre- to postseason change in RDI within the sample. Partial  $R^2$  values are provided to indicate the size of the overall effect, where  $R^2 \geq 0.01, 0.09,$  and  $0.25$  indicate small, moderate, and large effects, respectively. RDI, restricted diffusion imaging; PBM, photobiomodulation; BMI, body mass index; TBI, traumatic brain injury; FDR, false discovery rate.

pathophysiological effects of brain injury<sup>54</sup> and the high probability of exposure to RHAE throughout a season of American football, we hypothesized that RDI and QA would increase over the course of the season to a greater extent in the Sham PBM group, relative to the Active PBM group. As expected, we observed widespread increases in RDI and QA across the season in the Sham PBM group, consistent with an inflammatory response

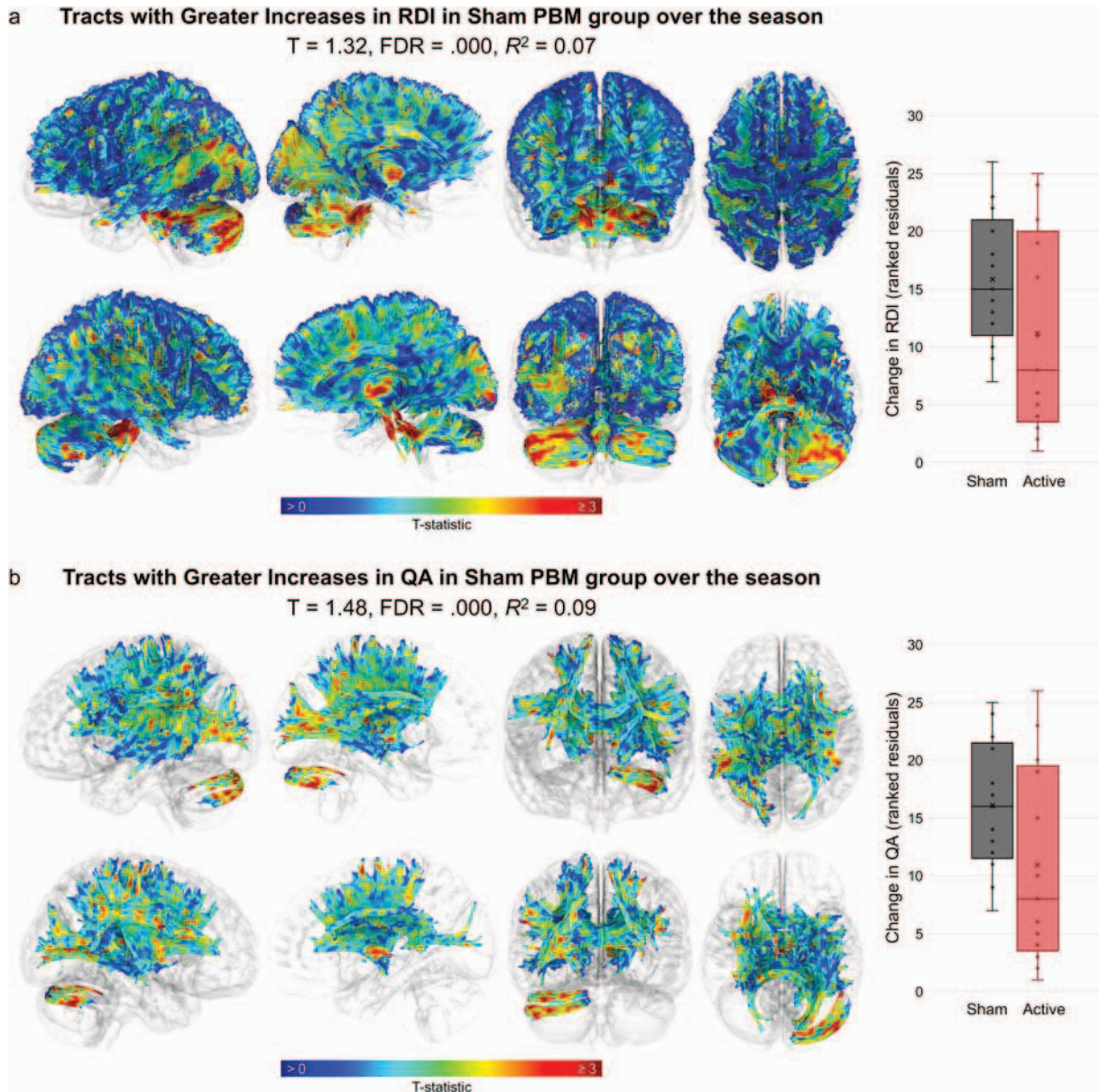
and subsequent axonal remodeling. Further supporting our hypothesis, athletes who received active PBM treatment exhibited relative stability in RDI and QA, with some white matter regions showing decreased RDI and QA over time. When preseason RDI/QA was included as a covariate in supplemental analyses, the apparent decreases in RDI and QA were no longer present or significant, respectively, in the Active PBM group; however,



**FIG. 5.** Longitudinal changes in QA within each group. Tracts with significantly increased QA from pre- to postseason are shown in the Sham (**a**) and Active (**b**) PBM groups. No tracts were found to have decreased QA in the Sham PBM group (**c**), whereas significant decreases in QA were observed across various tracts in the Active PBM group, particularly in the posterior left hemisphere (**d**). Results are shown in glass surface renderings from sagittal, coronal, and axial planes. The top rows depict left, anterior, and superior views, and right, anterior, and inferior views appear in the bottom rows. The color of the tract reflects the strength of the relationship, where small yet significant correlations are shown in dark blue, and large correlations appear in dark red. Spaghetti plots of subject-specific changes in ranked residuals of QA (effects of BMI and presence or absence of previous TBI removed) over time are provided for each significant within-group change in QA observed, where increases are plotted in red and decreases in blue. The black dashed line overlaid on each plot represents the average pre- to postseason change in QA within the sample. Partial  $R^2$  values are provided to indicate the size of the overall effect, where  $R^2 \geq 0.01, 0.09,$  and  $0.25$  indicate small, moderate, and large effects, respectively. QA, normalized quantitative anisotropy; PBM, photobiomodulation; BMI, body mass index; TBI, traumatic brain injury; FDR, false discovery rate.

the overall pattern of relative stability of RDI and QA remained. Overall, these findings suggest that PBM offers neuroprotection against RHAE-related brain changes and may play a role in reducing the negative effects of prior exposure to RHAE. By doing so, PBM may have the potential to mitigate the long-term neuropathological consequences of cumulative RHAE exposure in athletes, although additional longitudinal research is needed to determine this.

The observed increases in RDI and QA in the Sham PBM group are consistent with previous research indicating that RHAE exposure leads to neuroinflammation and axonal damage,<sup>15,18,19,104,105</sup> even over a single season of contact sport participation.<sup>106–108</sup> RDI elevations are associated with heightened immune cell infiltration,<sup>43,99</sup> while concurrent QA elevations may reflect ongoing repair of accumulated microstructural damage,



**FIG. 6.** Longitudinal changes in RDI and QA between Sham and Active PBM groups. Both RDI (**a**) and QA (**b**) increased over time to a significantly greater extent in the Sham PBM group, relative to the Active PBM group. Results are shown in glass surface renderings from sagittal (lateral), midsagittal (medial), coronal, and axial planes. The top rows of each panel depict left, anterior, and superior views, and right, anterior, and inferior views appear in the bottom rows. The color of the tract reflects the strength of the relationship, where small yet significant correlations are shown in dark blue, and large correlations appear in dark red. Box plots of group-specific changes in ranked residuals of RDI and QA (effects of BMI and TBI history removed) over time are provided. Partial  $R^2$  values are provided to indicate the size of the overall effect, where  $R^2 \geq 0.01$ , 0.09, and 0.25 indicate small, moderate, and large effects, respectively. RDI, restricted diffusion imaging; QA, normalized quantitative anisotropy; PBM, photobiomodulation; BMI, body mass index; TBI, traumatic brain injury; FDR, false discovery rate.

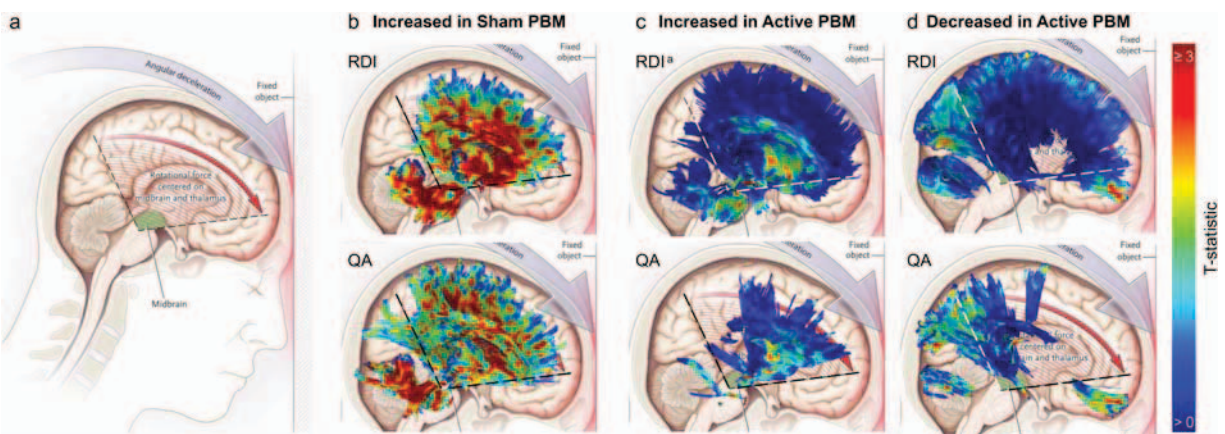
which activates in the presence of inflammation.<sup>24,25,28</sup> In contrast, the stability or reduction of these metrics in the Active PBM group suggests that the intervention

diminished the inflammatory response, potentially protecting against the neuropathological cascade that follows inflammation, which can involve neuronal damage

and death, impaired neuroplasticity, and long-term cognitive and mood effects.<sup>28</sup> These results are consistent with prior studies demonstrating PBM's anti-inflammatory effects across various biological systems,<sup>109–111</sup> including the brain.<sup>59,60</sup> PBM has also been shown to modulate inflammatory processes by regulating cytokine activity, reducing oxidative stress, and enhancing cellular metabolism, collectively supporting tissue resilience and repair.<sup>58–62,67</sup> Importantly, our findings suggest that consistent use of PBM may mitigate the acute inflammatory effects of RHAЕ within a single season and, if sustained across multiple seasons, could potentially reduce the cumulative burden of neuroinflammation that contributes to long-term neurodegenerative risk. However, longitudinal studies that follow athletes over multiple seasons are needed to directly test this possibility. Nonetheless, given that chronic neuroinflammation is implicated in the pathophysiology of conditions such as CTE,<sup>22,112</sup> our findings highlight the potential relevance of PBM as prevention strategy, further warranting longitudinal investigation into its role in long-term athlete brain health.

A key insight from our study is that the regions most affected by PBM treatment align with the identified “cone of vulnerability,”<sup>113</sup> which includes brain regions that are particularly vulnerable to mechanical strain and

shearing resulting from acceleration and deceleration forces associated with repetitive head trauma. These regions include the midbrain, brainstem, basal ganglia, thalamus, corpus callosum, peripheral association tracts, and association tracts with frontal and temporal lobe terminations.<sup>104,113,114</sup> Within the Sham PBM group, the areas with the greatest indication of inflammation and axonal repair almost exclusively fall within the cone of vulnerability (Fig. 7). Furthermore, in the Active PBM group, the regions that showed slight increases in RDI (nonsignificant) and QA (significant) are also within this area, while the areas with decreased RDI and QA fall largely outside of it, notably within portions of the posterior left hemisphere. This raises the possibility that PBM may facilitate recovery processes in previously affected regions. Specifically, we found the largest between-group differences in the middle cerebellar peduncle (midbrain), cerebellum, brainstem (corticospinal tract, medial lemniscus, dentatorubrothalamic tract, reticulospinal tract), corticostriatal pathways (basal ganglia), anterior and superior thalamic radiations, forceps major and minor of the corpus callosum, and several peripheral and fronto-temporal association tracts (inferior longitudinal fasciculus, uncinate fasciculus, arcuate fasciculus, cingulum bundle). The preferential effects of PBM observed in these regions suggest that prophylactic use of PBM may help preserve the integrity of structures that



**FIG. 7.** Cone of vulnerability. The first image portrays the “cone of vulnerability” to SRC (a). Midsagittal views of left hemisphere correlational tractography results from the longitudinal within-group analyses are overlaid onto the first image to demonstrate the correspondence of areas with increased RDI and QA within the Sham PBM group (b), the same pattern but to a much lesser extent in the Active PBM group (c), and the relative non-correspondence of areas with the greatest decrease in RDI and QA to the cone of variability in the Active PBM group (d). The color of the tract reflects the strength of the relationship, where small, yet significant correlations are shown in dark blue, and large correlations appear in dark red. SRC, sport-related concussion; RDI, restricted diffusion imaging; QA, normalized quantitative anisotropy; PBM, photobiomodulation. The first image (a) is reproduced with permission from Ropper and Gorson.<sup>113</sup>

<sup>a</sup>The increase in RDI observed within the Active PBM group was not statistically significant (FDR = 0.064).

are the most vulnerable to RHAЕ exposure. These findings emphasize the importance of further research to determine whether PBM can be leveraged as a targeted neuroprotective strategy for athletes with high RHAЕ exposure.

Our findings should also be considered in the broader context of existing neuroprotective strategies. Nutritional supplementation with long-chain omega-3 fatty acids, such as docosahexaenoic acid (DHA), attenuate neurofilament-light elevations across football seasons via membrane stabilization and anti-inflammatory effects.<sup>115</sup> In contrast, PBM acts directly at the cellular level by modulating mitochondrial cytochrome c oxidase activity, producing immediate effects on metabolism and inflammation and targeting multiple pathways simultaneously.<sup>58</sup> Equipment-based interventions, including advanced helmet technology and Guardian Caps, reduce macroscopic impact forces<sup>116,117</sup> but do not address the sub-cellular cascades that drive neuroinflammation. PBM may complement these approaches by enhancing tissue resilience once forces are transmitted. Pharmacological interventions have yielded mixed results in TBI populations and often carry systemic side effects,<sup>118–120</sup> limiting their utility in healthy athletes. Mechanistically, the present results extend the existing literature by demonstrating that PBM's effects are most prominent in regions within the cone of vulnerability, that stability of RDI suggests reduced immune cell infiltration, and that stability or reduction of QA is consistent with preserved axonal integrity. These findings collectively indicate that PBM may have the capacity to act prophylactically rather than purely as a reparative intervention and may therefore provide a distinct and complementary avenue for neuroprotection in athletes exposed to RHAЕ.

### Limitations and future directions

The sample size was small, limiting statistical power, the generalizability of the findings, and our ability to control for potential confounding variables. However, the use of permutation testing, the consistency of effects across multiple supplemental analytical approaches, and the anatomical plausibility of the affected brain regions support the robustness of our findings. Nonetheless, these results should be considered preliminary and hypothesis-generating, providing important groundwork for replication in larger cohorts and future multisite investigations designed to more definitively evaluate the effects of PBM in individuals exposed to RHAЕ.

Another limitation stems from our inability to report details regarding player position without risking compromise of the confidentiality of our participants. Recent work has demonstrated the importance of player position when considering the long-term sequelae of RHI,<sup>89,121–123</sup> and these findings are likely applicable to RHAЕ. The

frequency of impact, tissue strain magnitude, and time intervals between RHI exposures are related to the extent of metabolic, physiological, and structural alterations in the brain,<sup>12,108</sup> and these, in turn, are associated with functional outcomes.<sup>106,124,125</sup> The number, magnitude, strain, and location of RHI varies according to player position, where linemen experience more frequent, lower magnitude impacts with shorter time intervals, while speed-position players experience fewer, higher magnitude impacts with longer time intervals.<sup>89,123,126,127</sup> These differences have been shown to contribute to distinct patterns of structural and functional connectivity alterations,<sup>121,128</sup> even after a single season, suggesting cumulative neurological effects of RHAЕ. To assess the impact of exposure profile on change in RDI and QA over the season in the current sample, a supplementary analysis was performed within the Sham PBM group only. These results demonstrate significantly greater increases in RDI (Supplementary Fig. S9) and QA (Supplementary Fig. S10) over the season in players with high frequency/low strain positions relative to players with both moderate frequency/strain and low frequency/high strain positions. Given the similar distribution of exposure profiles, particularly of athletes in the high frequency/low strain profile, between the Active and Sham PBM groups, we do not expect these differences to have a meaningful impact on our findings. Nonetheless, these and previous findings emphasize the need for position-specific risk assessment and neuroprotective strategies to mitigate the long-term effects of repetitive head trauma in contact sports. Another relevant limitation of our study is that RHAЕ exposure was not assessed directly through collection of data on number of snaps, games played, starter status, or other detailed load metrics (e.g., accelerometer data), and we were therefore unable to control for potential group differences based on direct exposure. Direct assessment of RHAЕ exposure could provide insight into individual variability in response to PBM treatment, and future research should incorporate exposure data, including accelerometer-based head acceleration and impact monitoring, to refine our understanding of the relationship between player position, RHAЕ burden, PBM efficacy, and neuroinflammatory processes.

In addition, our sample did not include a noncontact or limited-contact sport comparison group, which limited our ability to conclusively attribute the observed neuroinflammatory and microstructural changes to RHAЕ exposure alone. A noncontact comparison group could have provided further validation of PBM's neuroprotective effects by determining whether the relative stability in RDI and QA observed in the Active PBM group was truly a protective effect against RHAЕ or if similar patterns occur in athletes who are not exposed to RHAЕ. Future studies should include a noncontact or limited-contact, low RHAЕ-exposure athlete comparison group

to determine whether there are differences in the effects of PBM dependent on RHAЕ exposures and improve the specificity of our findings. Moreover, while our study focused on a single season, the long-term effects of PBM on brain health across multiple athletic seasons remain unknown. Longitudinal studies could clarify whether PBM has cumulative neuroprotective benefits or if its effects diminish over time.

Beyond its neuroprotective properties, PBM may also promote functional improvements following RHAЕ exposure, likely by reducing neuroinflammation. Chronic neuroinflammation has been implicated in cognitive dysfunction, mood disturbances, disrupted sleep patterns, and poorer general health, all of which are common consequences of SRC and RHAЕ exposure.<sup>11,45,124,129,130</sup> By mitigating inflammatory responses, PBM may help preserve the neural circuitry critical for cognitive function, emotional regulation, and restorative sleep. Previous research supports the efficacy of transcranial PBM to enhance cognitive and motor function, improve sleep quality, and reduce symptoms of depression and anxiety in brain injured populations,<sup>74–80,85,86,131–134</sup> effects that are likely driven by its ability to reduce neuroinflammatory signaling, enhance mitochondrial function, increase cerebral blood flow, and facilitate neuroplasticity.<sup>48,52,54,60</sup> While this study did not assess functional outcome measures, it is possible that the neuroprotective effects we observed in the PBM group extend to behavioral and cognitive domains. Future research should examine whether the structural resilience conferred by PBM translates into immediate and long-term improvements in cognitive performance, emotional well-being, and overall neurological and physical health.

The optimization of PBM treatment protocols should also be considered in future research. The frequency of PBM use in this study (3 days per week) was based on manufacturer recommendations at the time, whereas updated guidelines now suggest more frequent use (5 to 6 days per week). The increased frequency of PBM usage could enhance the observed effects, potentially reducing inflammation in areas within the cone of vulnerability that showed slight increases over time in our PBM sample. Future studies should incorporate these updated protocols and explore newer PBM devices with additional targeting capabilities, such as direct cerebellar illumination. An additional consideration is that the reflection, absorption, scattering, and transportation of photons are affected by skin pigmentation, hair color, and hair type.<sup>135–139</sup> Some variability in the amount and rate of light energy reaching the brain tissue likely occurred in our sample due to individual differences in scalp contact and optical characteristics of the hair and skin. Future studies may benefit from implementing standardized methods to account for heterogeneity in

PBM delivery efficiency through optimizing dose parameters for maximal light penetration based on individual optical characteristics of head tissues.

### Clinical implications

Transcranial PBM represents a promising, noninvasive, and easily accessible intervention for mitigating the neurological consequences of RHAЕ in collision and contact sport athletes. PBM can be self-administered with minimal training, making it a feasible and cost-effective option for integration into athletic training programs. Importantly, any sports medicine personnel can be trained to administer PBM without the need for specialized clinical expertise, further enhancing its accessibility. Given the increasing awareness of the risks associated with cumulative RHAЕ exposure, implementation of potentially neuroprotective interventions is crucial for increasing sport safety and preserving brain health long-term. Although additional longitudinal research is needed to refine treatment protocols, PBM's ability to reduce neuroinflammation and promote structural resilience suggests it may not only prevent neurological damage but may also have the potential to improve long-term function in those with cumulative RHAЕ exposures. While sport is associated with a myriad of physical and psychological health benefits,<sup>140</sup> limiting the negative effects of RHAЕ exposure is of the utmost importance. As TBIs, and likely RHAЕ by association, have been identified as modifiable risk factors for unhealthy aging,<sup>141,142</sup> PBM may offer a safe and effective method for reducing neurotrauma-related risks in both the short- and long-term and for enhancing the safety of participation in collision and contact sports.

### Conclusion

This study provides compelling preliminary evidence that transcranial PBM protects against neuroinflammation and axonal injury in athletes exposed to RHAЕ during a single NCAA Division I American football season. These findings highlight the potential of PBM as a novel, noninvasive, neuroprotective intervention in collision and contact sports. By mitigating the microstructural changes associated with RHAЕ, PBM may reduce the risk of long-term neurological impairment and enhance the safety of sport participation. Future research should expand upon these findings by incorporating larger samples, long-term follow-up assessments, and functional outcome measures to further elucidate PBM's role in promoting brain health in athletes.

### Transparency, Rigor, and Reproducibility Summary

This study was not formally preregistered. It was an initial exploratory investigation—our first collaboration with the university football team—and conducted using

a novel, emerging technology. Due to the exploratory nature of the project, limited prior data, and uncertainty regarding effect sizes, the full analysis plan was not specified in advance. The study employed a prospective, double-blinded, randomized, sham-controlled design, with pre- and post-intervention assessments. A total of 40 team members (20 per group) were specified to be included. Sample size was determined by logistical constraints related to resources, time, and team availability rather than by a priori power analysis, as no comparable prior studies existed to inform a reliable effect size estimate. Of the 40 team members initially approached, 3 declined to participate, 2 were lost to follow-up, 4 were missing postseason diffusion data, 4 datasets did not pass quality control checks, and 1 dataset was excluded due to an incidental finding on imaging. A pseudorandom assignment method, using a random number generator, was used to balance group sizes, and participants were blinded to intervention condition. Participants were blinded to results of the imaging assessments throughout the study, even after clinical assessments were complete. Imaging quality control decisions and analyses were performed by investigators blinded to relevant characteristics of the participants. Imaging data were labeled using codes that were not linked to participant identifying information. All imaging data were collected using the same scanner (3T Siemens Tim Trio) and software version (syngo MR B17). All imaging datasets were preprocessed and analyzed at the same time. The time required for diffusion image acquisition was approximately 10 min. All other imaging parameters are presented in the Methods. Quality control of the preprocessing pipeline was assessed using eddyqc ([github.com/mabast85/eddy\\_qc\\_release](https://github.com/mabast85/eddy_qc_release)), and DSI Studio quality control protocols<sup>95</sup> were applied to the reconstructed data. All equipment and software used to perform acquisition are available from Siemens Medical Solutions USA, and all software used to perform processing and analysis are available from MRtrix ([mrtrix.org](https://mrtrix.org)), ANTs ([github.com/ANTsX/ANTs](https://github.com/ANTsX/ANTs)), FSL ([fsl.fmrib.ox.ac.uk/](https://fsl.fmrib.ox.ac.uk/)), and DSI Studio ([dsi-studio.labsolver.org/](https://dsi-studio.labsolver.org/)). The primary clinical outcome measures (QA, RDI) are established standards in the field.<sup>41–43,88</sup> The parametric statistical tests used were based on the assumptions of normality and homogeneity of variance, and nonparametric tests were used when these assumptions were violated. Missing data were handled using multiple imputation with predictive mean matching, as indicated in the text. Effect sizes have been reported in the main text for all outcomes. Control for multiple comparisons was performed using permutation testing and FDR procedures. No replication or external validation studies have been performed or are ongoing at this

time to our knowledge. The data will be made available by the corresponding author upon reasonable request. The code used to process and analyze these data is publicly available in our Open Science Framework data repository at <https://osf.io/94h8b/>. The authors agree to provide the full content of the article on request by contacting the corresponding author.

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### Authors' Contributions

Conceptualization: H.M.L., C.E., and E.A.W.; Data curation: H.M.L. and N.J.G.-H.; Formal analysis: H.M.L.; Funding acquisition: M.J.L., B.M., L.E.D., and L.S.C.; Investigation: M.J.L., P.K.J., B.M., W.D.A., L.D.T., M.H., and L.E.D.; Methodology: H.M.L., C.E., and E.A.W.; Project administration: M.J.L., B.M., D.F.T., and E.A.W.; Resources: M.J.L. and E.A.W.; Software: H.M.L.; Supervision: C.E. and E.A.W.; Validation: H.M.L., C.E., D.J., and E.A.W.; Visualization: H.M.L.; Writing—original draft: H.M.L., C.E., D.J., and E.A.W.; Writing—review and editing: H.M.L., C.E., D.J., M.J.L., P.K.J., F.K., M.R.N., N.J.G.-H., B.M., W.D.A., L.D.T., M.H., L.E.D., L.S.C., D.F.T., and E.A.W.

### Author Disclosure Statement

Dr. Lawrence Carr serves as a consultant for Vielight, Inc. All other authors declare no competing interests relevant to this study.

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### Supplementary Material

Supplementary Data

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