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Original Article

Neck Collar with Mild Jugular Vein Compression Ameliorates Brain Activation Changes during a Working Memory Task after a Season of High School Football

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Abstract

Emerging evidence indicates that repetitive head impacts, even at a sub-concussive level, may result in exacerbated or prolonged neurological deficits in athletes. This study aimed to: 1) quantify the effect of repetitive head impacts on the alteration of neuronal activity based on functional magnetic resonance imaging (fMRI) of working memory after a high school football season; and 2) determine whether a neck collar that applies mild jugular vein compression designed to reduce brain energy absorption in head impact through ‘‘slosh’’ mitigation can ameliorate the altered fMRI activation during a working memory task. Participants were recruited from local high school football teams with 27 and 25 athletes assigned to the non-collar and collar group, respectively. A standard N-Back task was used to engage working memory in the fMRI at both pre- and post-season. The two study groups experienced similar head impact frequency and magnitude during the season (all $p > 0.05$). fMRI blood oxygen level dependent (BOLD) signal response (a reflection of the neuronal activity level) during the working memory task increased significantly from pre- to post-season in the non-collar group (corrected $p < 0.05$), but not in the collar group. Areas displaying less activation change in the collar group (corrected $p < 0.05$) included the precuneus, inferior parietal cortex, and dorsal lateral prefrontal cortex. Additionally, BOLD response in the non-collar group increased significantly in direct association with the total number of impacts and total g-force ($p < 0.05$). Our data provide initial neuroimaging evidence for the effect of repetitive head impacts on the working memory related brain activity, as well as a potential protective effect that resulted from the use of the purported brain slosh reducing neck collar in contact sports.

Keywords: fMRI; football head impact; N-Back task; neck collar; working memory

Introduction

SPORTS-RELATED mild traumatic brain injury (sTBI) has been recognized as a significant public health problem.[1–3] On a broader level, emerging evidence now indicates that even seemingly mild concussions may result in exacerbated or prolonged neurological deficits.[4] However, effects of sub-concussive impacts, that is, impacts that do not induce symptoms or lead to missed time (the vast majority of impacts during practices and games) are largely unknown. Likewise, the mechanism underpinning the potential effect of these repetitive impacts on neurological outcomes is not fully understood. The high recurrence rate of clinically diagnosed concussion, and even brain microstructure alterations following an asymptomatic impact, especially in youth sports,[5–7] combined with the poor long-term prognosis, indicate that effective prevention strategies are needed to reduce the long-term effects of repetitive head impacts often experienced in athletics.

In a recent longitudinal neuroimaging study, diffusion tensor imaging (DTI) was used to evaluate the effect of a novel preventative strategy on the change of white matter (WM) structural

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integrity in high school athletes during a hockey season.[8] A specially designed neck collar was used to apply mild jugular vein compression to influence mild cerebral venous engorgement, which was expected to reduce head impact energy absorption and ''brain slosh'' injury during collision. Athletes who wore the collar when exposed to head impacts demonstrated significantly smaller longitudinal microstructural WM changes than those observed who did not wear the collar. This potential protective effect of collar wearing was also supported in a subsequent study in American high school football athletes (which was the same cohort as reported in the present study),[9] a contact sport with a high rate of collision and concussion.[10–12] The neck collar device was, again, found to ameliorate WM changes derived from DTI after a full season of competitive practices and games. Interestingly, the change in WM integrity in the non-collar group was found to have a significant association with the head impacts experienced during the season, suggesting a potential protective effect against head injury resulting from symptomatic and/or asymptomatic impacts.

In the present study, we aim to investigate the effect of jugular vein compression applied via a neck collar, during head impact exposure, to ameliorate potential functional deficits in working memory based on functional MRI (fMRI). fMRI is a non-invasive tool based on the blood oxygen level dependent (BOLD) signal that allows quantitative assessment of neural activity in response to task demands. More specifically, the hemodynamic response during the performance of a task can lead to an alteration of the de-oxygenated hemoglobin/oxygenated hemoglobin ratio in the regional blood vessels that support the corresponding neuronal activity. The difference of the ratio between the task and baseline stage determines the difference in MR susceptibility, which in turn can be translated into the MR signal used in fMRI that indirectly reflects the level of neuronal activity in the brain required to complete the task. fMRI has been used to elucidate underlying neuropathology in various diseases and disorders. Working memory is a common domain of deficit or impairment seen in patients with TBI and athletes with sports related concussion. It refers to the cognitive process in which information can be maintained briefly in memory and kept ready for subsequent retrieval and manipulation.[13,14] To engage working memory in fMRI studies, an N-Back task has frequently been employed.[15–18]

Based on fMRI, extensive evidence has shown significantly abnormal brain activation patterns based on BOLD signal in various brain regions associated with the performance of working memory tasks in patients with mild TBI[19–21] and moderate or severe TBI.[21–23] The most common brain areas reported to show abnormal activation patterns in these studies included the dorsolateral and ventrolateral prefrontal cortex, the supplementary motor and premotor areas, and the posterior parietal area. More recently, fMRI of working memory has been used in the research of contact sports. Although still at an early stage, with discrepancies remaining among different studies, accumulating evidence of fMRI of working memory has documented significant changes in the BOLD-activation patterns in a number of athlete cohorts, including those who suffered from clinically symptomatic concussions and those who experienced repetitive asymptomatic impacts after a season of competitive contact sports.[5,24] Studies have demonstrated increased or decreased activation after concussion or repetitive asymptomatic impacts, which are correlated with neurological testing documenting deficits in working memory.[14,25–27]

In the present study, we report a longitudinal fMRI study of working memory in high school football athletes. Using a longitudinal (pre- and post-season) design, we assessed changes in BOLD effect (brain activation) in response to working memory tasks at post-season compared with the brain activation prior to the beginning of the season. The effect of collar wearing was quantified based on the group difference of pre- to post-season change in brain activation between those athletes who wore the collar versus those who did not wear the collar. In addition, we also assessed the association between the pre- to post-season change in fMRI of working memory and the repetitive impacts experienced during the season. We evaluated the following hypotheses: 1) brain activation of working memory will change significantly in high school football athletes following one season, 2) collar wearing will ameliorate the changes in brain activation of working memory, and 3) the change in brain activation of working memory in the non-collar group will be significantly correlated to the number of impacts experienced during the season.

Methods

Participants

The study was approved by the Institutional Review Board and parental informed consent and participant assent were obtained. All participants were male athletes recruited from two local high school football teams. Sixty-two participants were initially enrolled and randomly assigned to two study groups: 30 in the non-collar group and 32 in the collar group. Inclusion criteria required participants to be able to provide written consent, be at least 14 years old, and participate on a varsity level high school football team. Among the 30 participants initially assigned to the non-collar group, four participants were excluded for missing pre- or post-season fMRI data and one participant was excluded after he experienced a season-ending anterior cruciate ligament (ACL) injury early in the season. Among the 32 participants initially assigned to the collar group, one participant had metal orthodontics and was unable to complete MR imaging, three participants complied only part of the season (66.7%, 39.7%, 89.6%, defined as the number of sessions [games and practices] attended [wearing the collar] divided by the number of potential sessions) and were excluded from the final analysis. One participant experienced a season-ending ACL injury early in the season and was excluded from the study, and two participants did not wear the collar throughout the entire season, and therefore were re-assigned to the non-collar group. In the final data analysis (Fig. 1), the non-collar group and collar group comprised 27 and 25 participants, respectively.

Study procedures

The study was a prospective longitudinal pre- and post-season study design. All subjects underwent an MRI scan at baseline (preseason) and again at post-season. A certified athletic trainer (AT) observed the participants throughout the competitive sports season and compliance of collar wear was monitored for both practices and games.

Impact surveillance and quantification

All participants wore a helmet during all games and practices. The inside of each participant's helmet was affixed with a GForce Tracker™ (GFT) (GForceTracker, Markham, Ontario) accelerometer device. The GFT allowed for the measurement of three axes of linear acceleration and three axes of angular velocity to calculate forces imparted to the head. Head impacts were recorded for all games and practices during the competitive season.

N-Back working memory fMRI paradigm

All participants performed a working memory N-Back task ($n = 0$, 2) during both the pre- and post-season fMRI assessments.

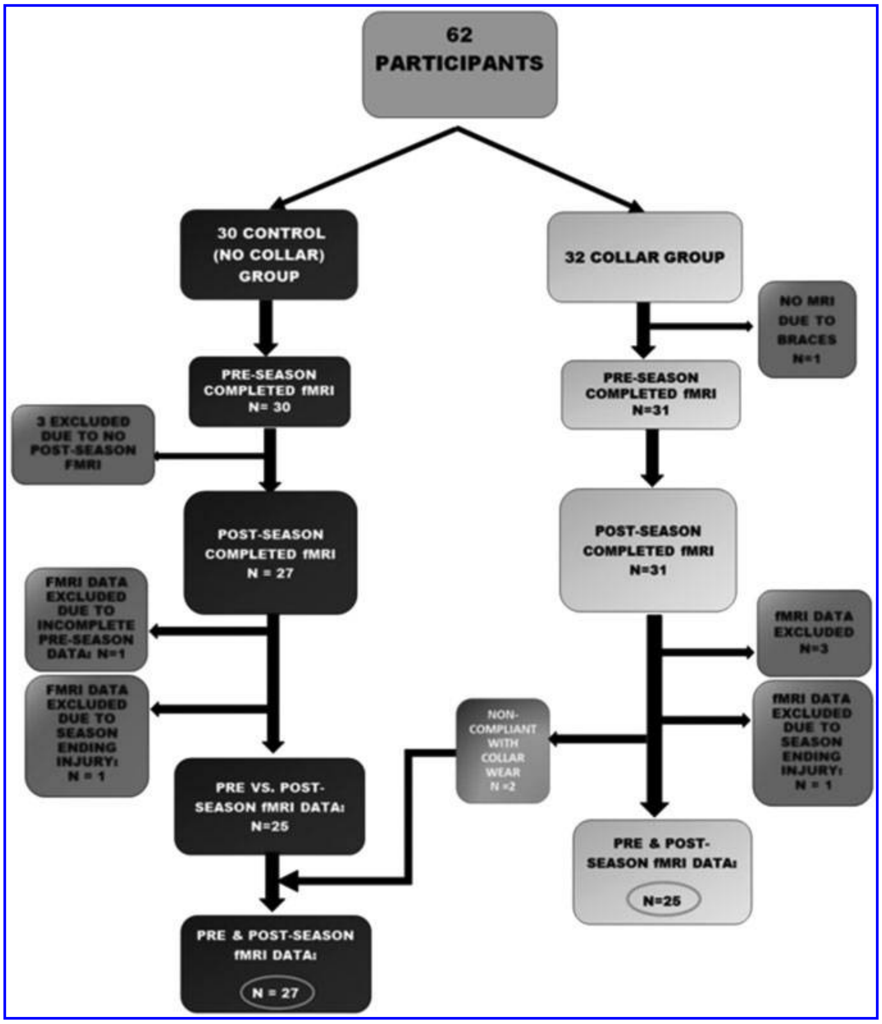

FIG. 1. Study participant flow chart.

This task was chosen as it has been shown to engage working memory function and is sensitive to alterations in memory after brain injury, with change in brain BOLD signal during task correlating with injury severity.[14,25–28] The fMRI experimental paradigm followed a standard block periodic design, which consisted of five cycles of fixation (12 sec), 0-Back (26 sec), and 2-Back (26 sec) periods. Therefore, each cycle (one fixation period + one 0-Back period + one 2-Back period) lasted 64 sec and the overall experiment lasted 5 min 20 sec. During the 0-Back period, a series of letters, including A, B, C, D, and O, was displayed on the screen in a random order. Each letter was displayed for 1.5 sec before the next letter appeared. Participants were required to respond by pressing a button when he/she saw the letter ''O.'' Participants were instructed not to press the button for any letters other than ''O'' during this task period. During the 2-Back task period, a series of letters, including A, B, C, and D, were displayed on the screen, one at a time, with each letter displayed for 1.5 sec, in a random order. The participants were instructed to respond by pressing a button when he saw a letter that was the same letter that was shown two letters ago. For example, if the letters appeared in the order of A-C-D-C, the participant needed to press the push button when he saw the second ''C'' because this was the same letter as the one shown two letters before it (2-Back). During the fixation period, a ''+'' sign was displayed in the middle of the screen. The participants were instructed to look at the ''+'' sign and do not respond during this period until switching to the next task period.

N-Back task performance

The button responses of the 2-Back tasks and 0-Back tasks were recorded in 15/27 athletes in the non-collar group and 12/25 athletes in the collar group during both pre- and post-season fMRI scans. Task performance indices included: (1) the accuracy of the 0-Back task and the 2-Back task responses, both defined as the percentage of correct button pressing in response to the task among the total number of responses; and (2) the response time (the time between the beginning of letter display and the time when the button is pressed) in response to the 0-Back task and the 2-Back task.

Description of the neck collar

In the present study, a neck collar was applied in the collar group to assess its potential effect on ameliorating changes in the brain activation compared with the non-collar group. The neck collar used was a specially designed device that applied mild jugular vein compression, which is postulated to result in slight cerebral venous engorgement and reduction of head impact energy absorption and brain slosh injury during collision. The term ''slosh'' refers to the movement of the brain within the space of the skull (while there is no connection between the two) during which the brain will absorb the energy of the movement and therefore subject it to potential injury. The mechanism of protection could be the ability of the gentle jugular vein compression, with its inherent mild impedance to jugular outflow, to create a mild engorgement of the venous capacitance vessels in the brain. This engorgement mimics the actions of airbags and bubble wrap in that less sloshing of fluids can occur, which reduces differential tissue densities from accelerating and decelerating at different rates, thus less damage/energy can be absorbed.[29] The collar size for each athlete was determined from the measured neck circumference. An ultrasound image was acquired during the fitting. A registered vascular technologist reviewed the ultrasound image to validate the proper collar setup and the internal jugular vein dilation after the collar was put on. A more detailed description about the collar fitting (and physiology) has been reported in previous work.[8,9]

MRI image acquisition

MR images were all acquired on a 3T Phillips Achieva scanner with a 32-channel, phase array head coil. A single shot echo planar imaging (EPI) sequence was used for fMRI data acquisition with the following specifications: repetition time (TR)/echo time (TE) = 2000/3.5 msec; field of view (FOV) = 240 × 240 mm; matrix = 64 × 64; in-plane resolution = 3.75 × 3.75 mm, slice thickness = 5 mm; number of slices = 38. A MPRAGE sequence was used to acquire high-resolution three-dimensional (3D) T1-weighted images (sagittal): TR/TE = 8.3/3.7 msec; FOV = 256 × 256 mm; matrix = 256 × 256; in-plane resolution = 1 × 1 mm; slice thickness = 1 mm; number of slices = 180.

Image data processing and analysis

Analysis of fMRI of working memory was performed with the FSL (FMRIB Software Library) (www.fmrib.ox.ac.uk/fsl) and AFNI (Analysis of Functional Neuroimages) software package.[30–32]

The first steps for the functional data processing and analysis, which included reorientation, brain extraction, and slice timing correction, were performed using FSL's *fslreorient2std*, *BET,*[33] and *slicetimer*. All fMRI frames were then aligned to the mean using FSL's *mcflirt.*[34] Outlying frames were identified using motion and intensity artifacts with FSL's *fsl_motion_outliers*. The functional images were then normalized to the MNI 152 template[35] by combining the transformation matrix from co-registering to the participant's anatomical scan using FSL's *flirt*[34,36] and the matrix from normalizing the anatomical scan to the MNI template. Motion artifacts in the functional data were regressed out of the data using a 24 parameter motion model (six motion parameters, the six motion parameters squared, a first order autoregressive model of the six motion parameters, and a first order autoregressive model of the six motion parameters squared) along with an additional parameter for each outlying volume.[37] The residuals from the motion regression were then bandpass filtered from 0.01 to 0.1 Hz and smoothed with a 6-mm (FWHM) Gaussian filter using AFNI's *3dBandpass*. The last step in the first level processing used FSL's *flameo* along with the N-Back design to generate the desired 2-Back verus 0-Back contrasts.

To generate the group activation map for the 2-Back versus 0-Back contrast across all 52 participants at baseline, the contrast and variance images from individual subjects were concatenated and used in FSL's FLAME mixed effect model (FMRIB's Local Analysis of Mixed Effects, model 1) followed by multiple comparison correction using FSL's *randomise* with 5000 permutations based on the threshold-free cluster enhancement (TFCE) approach.[38,39] Group comparisons, including longitudinal changes between pre- and post-season task related fMRI activation in the two study groups, and the group difference of this longitudinal change, were also processed and analyzed in FSL using FLAME with multiple comparisons corrected by FSL's *randomise*. In the correlation analysis, the brain areas that showed significant group difference in pre- to post-season change were used as a mask from which the difference in the pre- and post-season Z values of the athletes in the non-collar group were correlated with the impact variable using a Pearson correlation analysis. Additional correlation analyses with the impact data were also performed in the non-collar group using the pre- to post-season difference in Z statistics in individual clusters based on the segmentation of the previously mentioned mask with the AAL atlas.[40] Further exploratory analysis was also performed to investigate the correlation between the change in the fMRI BOLD response and the impact experienced at different times relative to the post-season imaging.

Intent-to-treat (ITT) analysis

In addition to the analysis based on Per Protocol design, we also conducted analyses based on the intent to treatment (ITT) principle using the original allocation regardless of an individual's compliance level. Thus, the three participants who were excluded from the collar group due to incomplete compliance in the Per Protocol analysis remained in the collar group. In addition, the two participants who were reassigned to the non-collar group from the collar group, because they didn't wear the collar throughout the season, also remained in the collar group according to the ITT protocol. As expected, similar but reduced effects were observed when the ITT analyses were used. The details of the ITT analyses are described briefly in the Results section. A more detailed description about the ITT results is included in the Supplementary Appendix for comparison.

Results

Participants characteristics

No statistically significant difference was found between the 52 participants who were included in the final analyses (17.22 ± 0.72 years) and those excluded participants (17.20 ± 0.76 years). For the 52 participants who were included in the final analyses (Table 1), no significant group difference in age at baseline imaging was noted (non-collar group: 17.34 ± 0.76 years; collar group: 17.0 2 ± 0.66 years; $p = 0.12$). The range, median, mean, standard deviation, and the t test statistical values can all be found in Table 1. Figure 2 shows that the number of impacts experienced during the season was similar between the two study groups across all g-force levels.

fMRI brain activation of N-Back working memory

Figure 3 presents the composite Z score map of brain activation during the pre-season N-Back fMRI experiment in the entire sample ($n = 52$; 27 athletes from the non-collar group, 25 from the collar group). Significant activation was defined as $p < 0.05$ after correction for multiple comparisons based on permutation (TFCE approach) testing. Both significant positive (in yellow-red, 2-Back >0 Back, neuronal activity required to complete the 2-Back task is greater than that for 0-Back task) and negative (in blue/light blue, 0-Back >2-Back, neuronal activity required to complete the 2-Back task is lower than that for 0-Back task) regions of activation were found.

Longitudinal pre- to post-season change in brain activation of N-Back working memory

Figure 4 presents the composite p value map for brain regions within the non-collar group that showed significantly stronger activation ($p < 0.05$ corrected) for the 2-Back >0-Back contrast at post-season when compared with the pre-season. No region was found to have stronger brain activation for the 2-Back >0-Back contrast at pre-season in comparison to that at post-season in the non-collar group. In the collar group, no significant longitudinal

Table 1. Participant Demographic Information and Impact Related Descriptive Statistics

	Non-collar (n = *27*)				*Collar* (n = *25*)						
	Range	*Median*	*Mean*	*SD*	*Range*	*Median*	*Mean*	*SD*	t	df	p
Age	16.01–18.33	17.63	17.34	0.76	15.50–18.17	17.13	17.08	0.66	1.59	50	0.12
Gender		All male				All male				-	
Body weight (kg)	64.20–122.20	91	92.41	16.69	57.2–134.5	83.7	87.48	18.63	1.01	50	0.32
BMI	21.20–36.50	27.50	27.97	4.60	20.00–42.00	25.70	26.83	4.87	0.85	47	0.40
Time btw imaging	96–154	128	128.41	14.27	95–153	133	130	16.52	0.37	50	0.71
Total hits											
>10 *g*	523–5241	1758	2083	1284	213–4954	1716	2025	1227	0.28	49	0.78
>20 *g*	211–2438	660	844	581.3	110–2288	767	862.67	503.92	0.33	49	0.74
>50 *g*	36–362	89	137	99.4	40–519	141	162.75	121.30	0.96	49	0.34
>100 *g*	2–48	9	14	10.6	2–77	16	19.57	19.05	0.67	48	0.51
Total *g*-force											
>10 *g*	13591–128006	39901	49047	31117	6672–131776	42902	49597	29242	0.10	49	0.92
>20 *g*	8005–86016	23035	30909	21051	5142–91708	28410	32703	19915	0.51	49	0.61
>50 *g*	2504–28632	6734	9972	7233	2708–39309	10615	11775	9077	0.83	49	0.41
>100 *g*	284–6458	1178	1847	1420	242–9023	1887	2310	2275	0.33	48	0.74
Average *g*-force/hit											
>10 *g*	18.63–27.53	23.4	23.5	2.36	16.26–34.69	24.74	25.38	3.89	1.09	49	0.28
>20 *g*	31.19–40.96	37.26	36.86	2.96	32.34–47.30	36.60	38.10	4.06	0.09	49	0.93
>50 *g*	64.61–81.20	72.88	72.69	4.23	60.34–82.25	71.46	71.22	5.10	1.14	49	0.26
>100 *g*	104.70–142.08	124.01	125.42	9.75	26.50–139.25	124.89	120.01	21.81	0.01	48	0.99

$N = 25$ in non-collar group in BMI group comparison.
BMI, body mass index; SD, standard deviation.

change (pre-season > post-season or pre-season < post-season) was found for either 2-Back >0-Back contrast or 2-Back <0-Back contrast.

Group difference of longitudinal change in brain activation and its association with head impact

Significantly larger pre- to post-season changes in brain activation for the 2-Back >0-Back contrast were found in the non-collar group in comparison with the collar group ($p < 0.05$ corrected). Figure 5A presents the composite p value map that shows areas in the brain with significant increase in activation after the season for the 2-Back >0-Back contrast in the non-collar group using the longitudinal change in activation for the 2-Back >0-Back contrast in the collar group as the comparative control. These are the brain regions where the longitudinal pre- to post-season changes in the collar group were significantly lower than the pre- to post-season increase of brain activation found in the non-collar group. The brain areas with significant group difference (that is, the red/yellow region as shown in Fig. 5A) included primarily the precuneus, inferior parietal cortex (BA7, BA40), and dorsal lateral prefrontal cortex (BA9, BA46). Based on the AAL atlas (Tzourio-Mazoyer and colleagues[40]), these regions included: bilateral precuneus, superior parietal gurus, left inferior parietal gyrus, supramarginal gyrus, precentral gyrus, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, triangular gyrus, superior occipital gyrus, middle occipital gurus, and angular gyrus. The details of these 13 specific regions, including their location, cluster size, x/y/z coordinate of the centroid of each of the clusters, are included in Table 2.

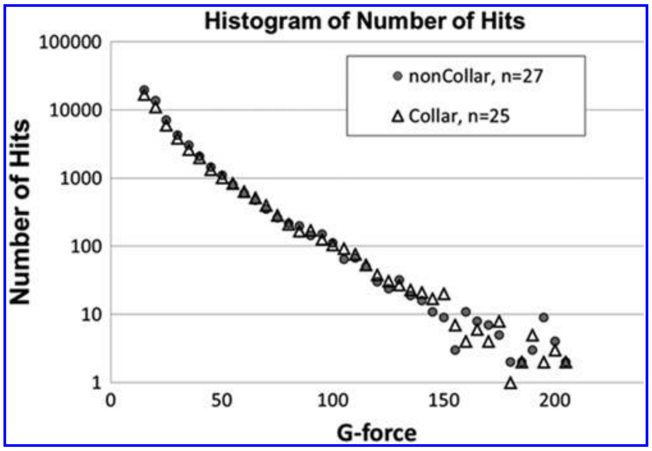

FIG. 2. Histograms showing the distribution of number of impacts at different g-force in the non-collar group in comparison with the collar group.

Within the brain areas with significant group difference of pre- to post-season change, the increase in the pre- to post-season change in brain activation (the overall area as shown in Fig. 4) in the non-collar group was correlated with the total number of impacts experienced during the season ($r = 0.43$, $n = 27$, $p = 0.028$, Fig. 5B). The correlation was not statistically significant in the collar group. In the non-collar group, 9 out of the 13 above-mentioned regions showed significant correlation between pre- to post-season change in fMRI BOLD signal and the total number of impacts or the cumulative g-force experienced during the season at various g-force thresholds. The correlation coefficients and the statistical significance between the change of brain activation in each of these sub-areas and the number of impacts and the cumulative g-force are provided in Table 2. No significant correlation was found between change in the fMRI BOLD signal and the average g-force (data not shown in the table).

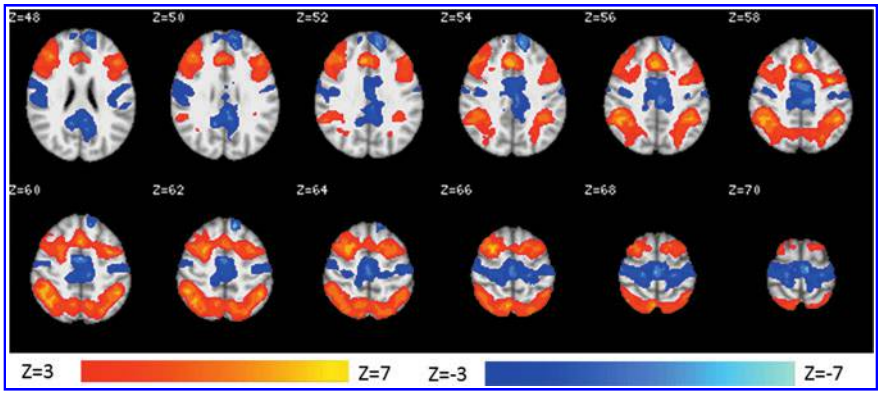

FIG. 3. Functional magnetic resonance imaging (fMRI) activation in all 52 participants (27 in non-collar group, 25 in collar group) at baseline ($Z > 3$, $p < 0.001$, corrected). The areas in red/yellow are regions with stronger brain activation during the performance of 2-Back task than 0-Back task. Blue/light blue areas are brain regions with stronger brain activation during the 0-Back task than the 2-Nack task. Image orientation is in radiological convention.

To explore the effect of the timing of impacts relative to the post-season imaging on the change of fMRI BOLD signal, the correlation coefficient between the impact related measures (number of hits, total *g*-force, average *g*-force) experienced at different times and the pre- to post-season change in brain activation was calculated for each individual week up to the last week prior to the post-season imaging. As shown in Figure 6A, the correlation coefficient for weekly number of hits was mostly high for the 10 individual weeks before the post-season imaging. The correlation coefficient for brain activation changes, relative to weekly impacts, was statistically significant or was at borderline to statistical significance in 8 out of these last 10 weeks. By comparison, the correlation coefficients were all low and non-significant in all the other earlier weeks indicating a temporal association between head impact and brain activation alterations. Similar contrast between the 10 weeks before the post-season imaging and the earlier weeks was also observed in the weekly total *g*-force (Fig. 6B) but not in the weekly average *g*-force (Fig. 6C).

fMRI N-back task performance

No significant difference between the non-collar group and the collar group was found in either the accuracy or response time at either time-point (Table 3). In the non-collar group, as expected, responses to the 2-Back tasks at pre-season were found to be significantly lower in accuracy and slower in response time (paired *t* test, $n = 15$, both $p < 0.0001$) than the responses to the 0-Back task. In the collar group, responses to the 2-Back tasks were also significantly lower in accuracy and slower in response time when compared with the responses to the 0-Back tasks (paired *t* test, $n = 18$, $p < 0.0001$, $p = 0.0150$, respectively). Similarly, at post-season, significantly lower accuracy and slower response were found in the 2-Back responses when compared with the 0-Back responses in both the non-collar group ($p = 0.0023$, $p = 0.0003$, respectively) and the collar group ($p = 0.0004$, $p = 0.0018$, respectively). No significant longitudinal pre- to post-season change was found in either accuracy or response time in either study group. For both study groups, the pre-season 0-Back vs. 2-Back difference did not change significantly when compared with post-season in both the accuracy and the response time.

Neuroimaging findings based on ITT protocol

The results based on the ITT protocol are similar to findings based on the Per Protocol design (Supplementary Figs. 1–4, Supplementary Tables 1, 2; see online supplementary material at

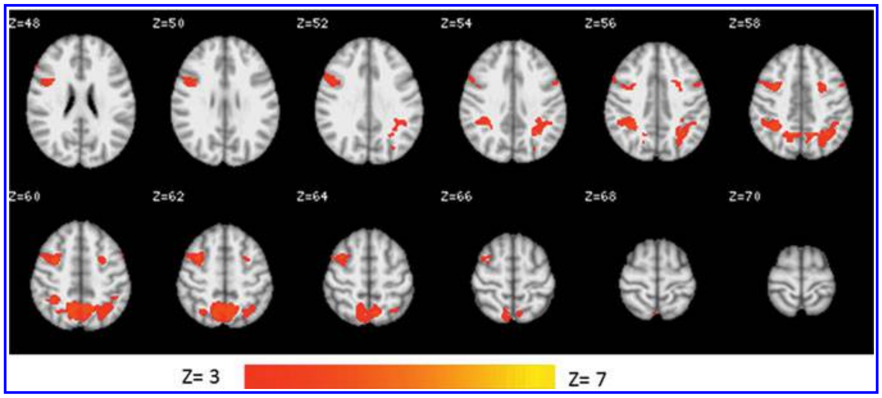

FIG. 4. Brain regions with significant pre- to post-season difference in functional magnetic resonance imaging (fMRI) activation in the non-collar group ($n = 27$). This analysis was performed using a mask based on the regions with significant brain activation for the 2-Back >0-Back contrast as calculated at baseline (pre-season). The ‘‘hot’’ regions are brain areas with significantly stronger activation at post-season than pre-season ($Z > 3$, $p < 0.05$ corrected). No significant pre- to post-season difference was found in collar group. Image orientation is in radiological convention.

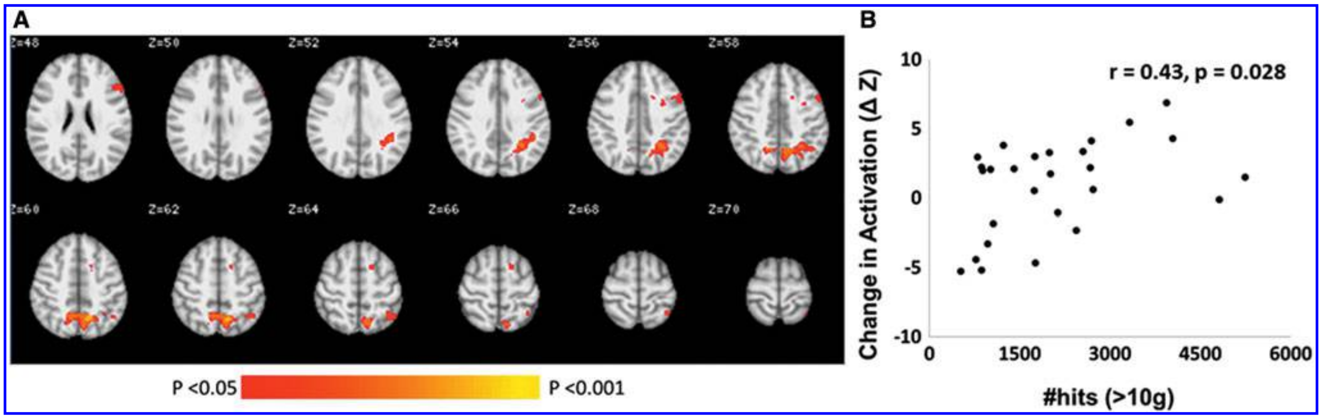

FIG. 5. **(A)** Composite *p* value map that shows brain regions with significant group difference in the pre- to post-season change for the 2-Back >0-Back contrast ($p < 0.05$, corrected, threshold-free cluster enhancement [TFCE]). The result is equivalent to the longitudinal changes in the non-collar group with the longitudinal changes in the collar group as the control. The main regions include the precuneus, inferior parietal cortex, and dorsal lateral prefrontal cortex. Image orientation is in orientation is in radiological convention. **(B)** Significant correlation between the total number of hits each athlete experienced during the season in the non-collar group and the pre- to post-season change of brain activation for the 2-Back >0-Back contrast. For these athletes in the non-collar group, the mean Z score value was extracted from the brain regions with significant group difference of longitudinal change (as in Fig. 4) at both time points. The difference in brain activation (ΔZ) was calculated as the Zpost – Zpre. Therefore a positive ΔZ means post-season activation is stronger than pre-season. The significant correlation shows that this increase in activation is associated with more hits experienced during the season.

http://www.liebertpub.com). Briefly, based on the ITT design, significant pre- to post-season increase in fMRI BOLD signal was found in the non-collar group but not in the collar group (Supplementary Fig. 3). The group difference of pre- to post-season increase in fMRI brain activation was statistically significant after using the collar group as the control (Supplementary Fig. 4A). However, the brain regions with significant group difference of longitudinal fMRI were smaller than that based on the Per Protocol design (Supplementary Table 2). Similar to the Per Protocol analysis, a significant correlation was also found in the ITT analysis between the increased fMRI BOLD signal and the number of total hits experienced during the season in the non-collar group but not in the collar group (Supplementary Fig. 4B). It should be noted that the smaller number of brain regions with significant group difference was expected due to the difference of compliance in the two study designs. In the ITT analysis, two non-compliant athletes and the three partially compliant athletes were included in the collar group. This heterogeneity introduced in the group analysis is expected to lead to more conservative findings. In the present study, the less significant findings from a ''diluted'' intervention provides additional support for an effect of collar wearing on pre- to post-season changes of fMRI activation during working memory.

Discussion

Prevention or reduction in sTBI incidence and severity will ultimately reduce public health costs and make sports participation significantly safer. Currently, primary prevention strategies for concussion are nearly absent or focus only on impact dispersion devices such as helmets.[41] This study sought to assess the effect of a jugular vein compressive collar to mitigate the change in fMRI activation during working memory tasks in athletes after experiencing repetitive head impacts for a full competitive high school football season. For the two study groups (collar vs. non-collar) with similar number of impacts, cumulative *g*-forces, and average *g*-force per impact during the season (all $p > 0.05$) we found that: (1) fMRI BOLD response during a working memory task was significantly stronger at post-season when compared with pre-season in the non-collar group (corrected $p < 0.05$), but not in the collar group; (2) significantly less pre- to post-season change in activation was found in a number of brain regions, including the precuneus, inferior parietal cortex, and dorsal lateral prefrontal cortex, in the collar group when compared with the non-collar group; (3) a significant increase in the pre- to post-season change of brain activation was seen in the non-collar group, but not in the collar group, as the total number of impacts increased, and 4) the changes in fMRI BOLD response in the non-collar group correlated with the timing of the impacts in relation to post-season imaging.

There has been a long held intellectual discussion in defining TBI by way of anatomical verses functional metrics and deficits. Previous research on patients with TBI shows a strong relationship between abnormalities in topological organization of brain networks and behavioral deficits.[42] Based on our pilot data, collar wearing was related to reduced alterations in neurophysiological outcomes measured in association with an auditory task.[8] These prior pre-clinical and clinical data indicate that it may be possible to protect the ''anatomical'' brain structure from head impact exposure with jugular impedance without any ''clinical/functional'' benefit.[8,9] Conversely, if a research modality is unable to differentiate a decline in functional parameters, there still may be an anatomical injury that is not severe enough or have accumulated enough for overt symptoms to be present. To date, pre-clinical studies have demonstrated anatomical preservation due to jugular compression during repetitive cranial impacts. An 83% reduction in amyloid precursor proteins (a signature indicator of axonal injury) was demonstrated in rats utilizing jugular compression during a 900 *g*-force impact model.[29] Previous early-phase clinical trials have shown a statistically significant change in DTI measures (a potential biomarker for injury) in the brains of high school hockey and football players during a season of contact sport (the latter with the same cohort as in the present study).[8,9] Notably, one of the studies included an arm whereby the Brain Network Activation score, a

Table 2. Brain Regions with Significant Group Difference Based on the Comparison of Pre- to Post-Season Change in fMRI Working Memory Brain Activation between the Two Study Groups

	Voxels	*Centroid coordinate (x,y,z)*	*Number of hits*				*Cumulative g-force*			
			>10 g	*>20* g	*>50* g	*>100* g	*>10* g	*>20* g	*>50* g	*>100* g
Left hemisphere										
PCUN	455	(–8,–63,50)	–0.378(ns)	–0.336(ns)	–0.408(0.035)	–0.425(0.027)	–0.382(0.049)	–0.367(ns)	–0.425(0.027)	–0.436(0.023)
SPG	182	(–23,–59,50)	–0.379(ns)	–0.373(ns)	–0.438(0.022)	–0.439(0.022)	–0.400(0.039)	–0.404(0.037)	–0.446(0.020)	–0.436(0.023)
IPG	332	(–36,–54,45)	–0.359(ns)	–0.311(ns)	–0.341(ns)	–0.359(ns)	–0.353(ns)	–0.331(ns)	–0.351(ns)	–0.358(ns)
SMG	14	(–45,–41,33)	–0.364(ns)	–0.349(ns)	–0.323(ns)	–0.290(ns)	–0.366(ns)	–0.356(ns)	–0.325(ns)	–0.2936(ns)
PreCG	73	(–49,8,41)	–0.371(ns)	–0.318(ns)	–0.312(ns)	–0.312(ns)	–0.357(ns)	–0.330(ns)	–0.317(ns)	–0.306(ns)
SFG	56	(–16,8,56)	–0.422(0.028)	–0.398(0.040)	–0.445(0.020)	–0.436(0.023)	–0.432(0.024)	–0.422(0.028)	–0.451(0.018)	–0.422(0.028)
MFG	29	(–47,12,41)	–0.167(ns)	–0.121(ns)	–0.183(ns)	–0.300(ns)	–0.163(ns)	–0.146(ns)	–0.210(ns)	–0.316(ns)
IFGtri	149	(–50,24,22)	–0.365(ns)	–0.293(ns)	–0.397(0.040)	–0.408(0.035)	–0.357(ns)	–0.329(ns)	–0.414(0.032)	–0.395(0.041)
SOG	1	(–16,–64,38)	–0.437(0.023)	–0.412(0.033)	–0.334(ns)	–0.204(ns)	–0.424(0.028)	–0.404(0.037)	–0.312(ns)	–0.214(ns)
MOG	36	(–24,–59,37)	–0.380(ns)	–0.372(ns)	–0.353(ns)	–0.358(ns)	–0.387(0.046)	–0.381(0.050)	–0.355(ns)	–0.368(ns)
AG	54	(–35,–54,38)	–0.406(0.036)	–0.358(ns)	–0.339(ns)	–0.320(ns)	–0.393(0.043)	–0.365(ns)	–0.340(ns)	–0.328(ns)
Right hemisphere										
PCUN	208	(10,–57,49)	–0.465(0.015)	–0.423(0.028)	–0.427(0.026)	–0.366(ns)	–0.460(0.016)	–0.437(0.023)	–0.430(0.025)	–0.378(ns)
SPG	6	(16,–66,50)	–0.485(0.010)	–0.497(0.008)	–0.462(0.015)	–0.294(ns)	–0.500(0.008)	–0.504(0.007)	–0.439(0.022)	–0.289(ns)

The anatomical structures for these specific regions were determined based on GM atlas in MNI space. The region name, size, x/y/z coordinates are included. The correlation coefficients between the change in fMRI working memory brain activation in athletes and the impact experienced in the non-collar group are also included for each of the sub-regions involved. The centroid coordinates are defined in mm in MNI space. Voxel size = 2 mm × 2 mm × 2 mm = 8 mm^3.

AG, angular gyrus; fMRI, functional magnetic resonance imaging; IFGtri, inferior frontal gyrus – triangular; IPG, inferior parietal gyrus; MFG, middle frontal gyrus; MOG, middle occipital gyrus; ns, not significant; PCUN, precuneus; PreCG, precentral gyrus; SFG, superior frontal gyrus; SMG, supramarginal gyrus; SOG, superior frontal gyrus; SPG, superior parietal gyrus.

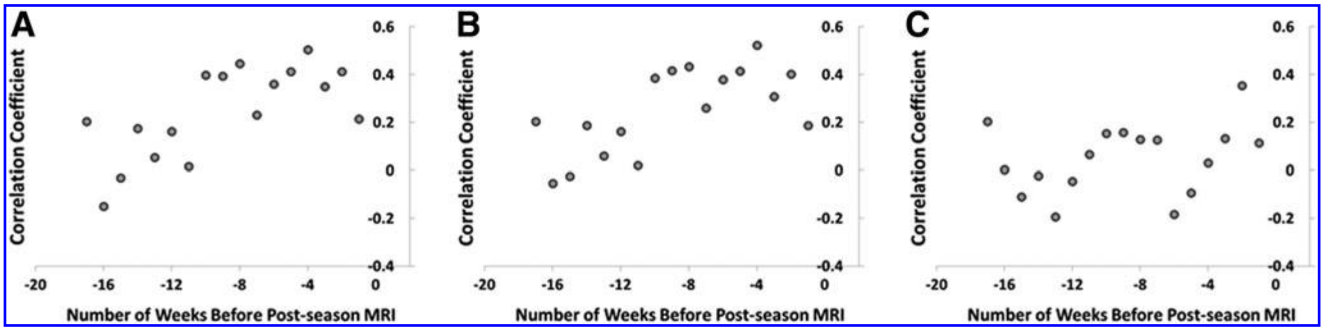

FIG. 6. Correlation coefficient between the pre- to post-season change of brain activation and the weekly impact (**A**: number of hits; **B**: total *g*-force; **C**: average *g*-force) experienced at different times prior to the post-season imaging. The X-axis denotes the week number before the post-season imaging, for example, −1 represents the last week, and −4 represents the 4th week prior to the post-season imaging. MRI, magnetic resonance imaging.

neurophysiological biomarker that quantifies the synchronization of brain electroencephalogram (EEG) electrophysiological activation, not only was protected from alteration with collar use, but in the no-collar wearing group EEG data were correlated with the change in WM structural integrity based on DTI.[8]

This brings us to the novelty and importance of the present study in which fMRI was combined with the testing of the effect of collar wearing. fMRI has been used to study the neuro-functional changes in TBI and/or sTBI.[19,20,24,27] In the present work fMRI was used to further study the effect of collar wearing after head impacts, adding a functional component to prior structural and physiological investigations. Our study included a cohort of youth athletes with mostly sub-concussive impacts without any signs or symptoms of brain injury. Based on the reaction time and accuracy measure acquired from a subset of the participants during the performance of N-Back task data, no significant neurocognitive functional deficits were found, and yet, significant alterations were noted in the brain activation at the end of the season in comparison with the pre-season in the non-collar group. Changes were also found to correlate with the impact load, suggesting that fMRI could be a sensitive tool to the initial functional changes in the physiological process in the brain in response to head impacts (which were mostly asymptomatic in the present study). As these alterations were only found in those subjects not wearing the collar, the results lend credence to the notion that jugular vein compression has the potential to protect against not only the structural and physiological alterations,[8,9] but also functional alterations associated with sub-concussive impacts.

fMRI of working memory using the N-Back task has been applied extensively in studying various neurological disorders and diseases. Functional deficits in working memory are often found to be affected in patients with TBI or in athletes with concussion or repetitive sub-concussive impacts.[14,19,20,23,24,27,43] In general, the most commonly reported brain regions that are affected based on fMRI during the performance of the N-Back task include the dorsolateral and ventrolateral prefrontal cortex, the supplementary motor and premotor areas, and the posterior parietal area (which are associated with working memory, spatial processing, attention, and executive function). The results of our study confirm previous findings (Fig. 4, Fig. 5A). Contrary to the general consensus regarding brain regions affected, the direction of change in brain activation in response to disturbance during the performance of the N-Back task has varied in different studies. Both hyper- or hypo-activation (stronger and weaker, respectively, activation) have been found in patients when compared with the controls.[14,25–27] For example, in a recent longitudinal study of sport-related concussion,[27] athletes were assessed at three different post-concussion time-points (3 days, 2 weeks, and 2 months). Compared with the controls, abnormally higher brain activation was found in dorsal lateral prefrontal cortex and inferior parietal cortex in the

Table 3. fMRI N-Back Task Performance

	Non-collar				*Collar*						
	Range	*Median*	*Mean*	*SD*	*Range*	*Median*	*Mean*	*SD*	t	df	P
0-Back – pre-season											
Accuracy (%)	90.00–100.00	95.00	94.63	1.92	85.00–100.00	95.00	95.83	3.19	1.65	49	0.10
Response time (msec)	430–630	492	502	52	455–670	508	521	57	1.22	49	0.23
2-Back – pre-season											
Accuracy (%)	76.19–100.00	85.71	85.71	6.49	80.95–95.24	90.48	88.89	4.32	1.67	31	0.10
Response time (msec)	468–822	584	618	116	445–874	557	575	109	0.83	31	0.41
0-Back – post-season											
Accuracy (%)	90.00–100.00	95.00	95.56	2.12	90.00–100.00	95.00	95.56	2.12	0.04	47	0.97
Response time (msec)	417–640	506	508	48	414–676	484	510	75	0.11	50	0.91
2-Back – post-season											
Accuracy (%)	47.62–100.00	85.71	88.71	10.82	76.19–100.00	90.47	90.01	6.44	0.55	50	0.58
Response time (msec)	443–763	576	575	87.65	419–710	559	555	69	0.91	50	0.37

fMRI, functional magnetic resonance imanging; SD, standard deviation.

concussed athletes. Interestingly, the task performance of the concussed athletes during the N-Back experiment was not significantly different from the controls, suggesting that the fMRI is a sensitive tool to detect the neuronal response despite the negative findings in outcome assessment. In a study of minor brain injury,[14] patients were found to have increased brain BOLD signal during the performance of working memory task and the increase was found to correlate with injury severity based on post-concussion symptom evaluation.

In distinction to the hyper-activation in patients found in these two studies, as well as in several other studies, hypo-activation has also been reported in the literature.[23,25,26] For example, Chen and associates showed significantly reduced task related brain activation in athletes at post-concussion in dorsolateral prefrontal cortex in comparison with the controls and they also reported significant correlation between the reduction of fMRI BOLD signal and the post-concussion index score.[25,26] Our results are in line with the studies that showed stronger fMRI BOLD signal of working memory in cohorts with disturbance to brain network. It should be noted that the increase of brain activation observed in the non-collar group in the present study was based on a longitudinal comparison, that is, pre- and post-season differences within the same study group, rather than in comparison to normal controls. In fact, the cross-sectional comparison between the non-collar and collar group at post-season did not yield any significant findings, and yet the longitudinal comparison showed significantly increased brain activation in the non-collar group in the brain regions known to be involved in working memory. These subtle but significant changes within the ''un-protected'' group, that is, the non-collar group, at post-season may be a reflection of initial response of the brain to the repetitive asymptomatic impacts. Whether these changes will remain persistent and turn into more chronic and/or explicit abnormalities (functional, structural, and/or physiological) or even become clinically significant alterations warrant a long-term follow-up study.

This last point about the long-term progression of the changes observed immediately at the end of the season is particularly interesting and important because it taps into the neural mechanisms underpinning the changes, that is, whether the increase of BOLD signal during the performance of working memory task suggests additional recruitment of neural resources as a transient measure to compensate for the potentially compromised function, or whether the change suggests a more permanent re-organization in additional locations that involves structural and functional alterations related to the working memory network in the brain (including redistribution within the network). Both compensatory and re-organization theories have been discussed frequently in the interpretation of the BOLD signal change in fMRI research studies of various patient populations.[19,20,23,44–48] Relating to the data presented in this study, it is premature to determine whether the change observed in the present study is due to compensation or re-organization, although the locations of the pre- to post-season difference seem to be mostly within the brain network commonly known to be responsible for the working memory function, suggestive of a compensatory mechanism. However, this remains to be investigated in the future when longer term follow-up data become available.

The association of non-symptomatic impacts to either structural or functional imaging biomarkers have been reported in several recent studies.[5,24,49] In our previous study based on DTI, it was found that the change in diffusion coefficient in WM in the non-collar group within a season was significantly associated with impact load.[8,9] The functional results in the present study corroborate the previous structural findings, that is, the pre- to post-season increase in brain activation in the athletes in the non-collar group, when they were engaged in a working memory task, was significantly correlated with the total number of impacts and the cumulative total *g*-force experienced during the season. Interestingly, our data also showed that impacts experienced at different times preceding the imaging may have different levels of contribution to the BOLD signal change, with the impacts experienced at times closer to the post-season imaging showing greater correlation (Fig. 6). As Bazarian and colleagues previously detailed,[5] ''… (at the time of post-season imaging), each injured brain area will be in unique and possibly different stages in the evolution of traumatic axonal injury and/or repair. Thus the DTI scan of the whole brain done at the end of the football season likely reflects a combination of the cellular events occurring in the injured brain regions which may be at different axonal injury stages.'' Although it was in the context of a DTI study, the comment about the importance of the timing of head impact remains valid. The more frequent significant correlations between changes in BOLD signal and weekly impact load at times closer to the post-season imaging may be a reflection of such a timing effect. It is unclear whether the low correlation during the earlier weeks (Fig. 6) suggests that the alteration of neurofunction seen at the end of the season is no longer under the influence of the early impact during the season.

It should be noted that it would be premature to conclude whether there is a causal relationship between the impact load and the microstructural and the neuro-functional changes, or between the functional and the structural changes, based on the findings in these athletes. Nevertheless, these findings lend support to the emerging literature that repetitive non-symptomatic impacts during sports may lead to subtle but significant alteration in brain networks. The findings from the current dataset, in combination with prior early clinical trials showing that mild jugular vein compression applied during head impact exposure can ameliorate alterations in brain structure, neurophysiology, and function, highlight the need for continued research on this mechanistic prevention approach.

The findings in the present study may have been limited by several factors. First, the authors acknowledge that fMRI has some inherit limitations, for example, variability in the hemodynamic response, brain blood volume, vasculature, and neurovascular coupling, as well as the poor temporal resolution as the results of MRI EPI sequence, which will all inevitably affect the variability and stability of the imaging data and the interpretation of the findings. fMRI BOLD signal is, by nature, not a direct and quantitative measure of neuronal activity and hence it is important in not overstating its implications and the need to subject all findings to statistical and power analysis. fMRI is also an indirect and qualitative measure of brain activity in response to the tasks performed by the study participants. fMRI is useful to help identify and localize brain regions engaged in the neural activity which, as the majority of fMRI studies, are qualitative in nature. Although the direct correlation between the fMRI BOLD response and underlying neural activity is an active area of research, the current results associating altered response to recent head impact only in the non-collar group highlight cognitive fMRI as potentially an important outcome to support the investigation of brain response to head impacts. Second, the current investigation showed differential responses to head impacts as evidenced by fMRI based alterations in brain activation. However, it should be noted that the significant group differences did not translate into differences in cognitive behavioral task performance. Although speculative, this may be due to the ceiling effect from the 2-Back task selected for the current investigation; future fMRI based investigations may consider including more challenging tasks, for example, using a 3-Back task, to help expose the potential neurocognitive deficits in the outcomes between collar and non-collared athletes exposed to head impacts. Third, it might be argued that the changes in fMRI BOLD signal observed in the non-collar group but not in the collar group need further investigation with comparison with additional control groups. We acknowledge that the current study results are limited without the inclusion of longitudinal comparisons of healthy control subjects without head impact exposure. Current investigations are underway with non-head impact, non-helmeted control groups to evaluate exercise effect and the potential baseline difference between the collision sports and non-collision sports and gender. Fourth, In the current investigation, every effort was made to maximize compliance with the collar intervention; however, there was an approximately 10% crossover rate from the ITT to Per Protocol analysis. Importantly, the significant effect of reduced brain alteration was noted in the collar group with an increased relative effect noted in the Per Protocol analysis. This relative increase in effect size noted in the Per Protocol relative to the ITT analysis indicates that the measured effect is associated with collar wear. Fifth, the significant correlations of fMRI changes and head impact exposures were only ''moderate'' in nature. Although larger sample size in future study design may help drive more conclusive associations, it is also possible that the ''moderate'' correlations observed in the present study are reflective of the dynamic alterations and recovery that is presumed to be associated with subconcussive head impact exposure throughout the competitive season. This hypothesis is supported by the significant association of effect of head impact timing on the correlations. The data indicating that the magnitude and statistical significance of the correlation remained consistently higher in the later weeks (but not in the early weeks) in the season, suggest a potential temporal progression of the change of neural activity in response to the repetitive head impacts.

The correlation coefficients between the changes of BOLD signal in the sub-regions in the brain versus the impact load were all moderate and did not survive multiple comparison correction. Therefore, only un-corrected data (correlation coefficient and *p* value in Table 2) were reported. Larger sample sizes in future studies will help to localize those areas with the most significant association and thus improve the understanding of the neural mechanism underlying these changes. Systematic efforts were undertaken to standardize measurement of head impacts between study groups and optimize data collection; the authors acknowledge the potential for spurious head impact measurement with accelerometry (e.g., pounding helmet on ground while not on head). However, the selection of similar teams and having two spotters at each game and practice helped to mitigate the measurement of spurious data collection and ensures the relative error was consistent between study groups. Whereas prior validation models indicate that GFT can provide suitable impact monitoring when worn in helmets, the authors acknowledge the potential for 10–40% error in accelerometery measures with GFT.[50,51] Further efforts to achieve algorithmic solutions to accelerometry measurement error are needed. It should be noted that the limited sample size in this study did not allow for controlling for the between-subject difference in impact load related to the position each athlete played in the field. The current investigation was focused on the assessment of objective biomarkers that are associated with brain functional integrity, therefore the sample size and study design were not appropriate to evaluate the subjective and often nebulous outcome of clinically diagnosed ''concussion.'' The authors acknowledge future large-scale epidemiological clinical trials are needed to determine the potential of the investigated collar device for mitigating clinically diagnosed concussion incidence. Due to the logistical difficulties with subject based randomization, the current study randomized at a team level potentially incurring bias related to competition, socioeconomic class, or other factors. Although the two local high schools selected for the study were highly compatible, and the impact loads were similar between the two teams, we cannot exclude the possibility that the group difference in the change of fMRI BOLD signal may be attributed to the other factors associated with the group categorization in addition to the collar wearing. Lastly and most importantly, future studies may benefit from including behavioral and neuropsychological assessment as part of the outcome evaluation in association with the neuroimaging findings.

Conclusion

Wearing a mild jugular venous compression neck collar during a season of high school football resulted in significantly smaller pre- to post-season changes in brain activation during a working memory task when compared with those not wearing the collar. Combined with the significant correlation found between changes in brain activation and impact load in the non-collar group, our results suggest a potential neural protective effect of this intervention that may be related to intracranial venous engorgement and decrease of slosh related injury. Although further investigation is warranted, this novel brain injury prevention device may potentially serve as an alternative approach in reducing cognitive morbidity in youth participating in contact sports.

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Author Disclosure Statement

David Smith is the inventor of the Q-Collar approach and has financial interest in the results of the current research.

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