Mild Jugular Compression Collar Ameliorated Changes in Brain Activation of Working Memory after One Soccer Season in Female High School Athletes

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Abstract

Recent neuroimaging studies have suggested that repetitive subconcussive head impacts, even after only one sport season, may lead to pre- to post-season structural and functional alterations in male high school football athletes. However, data on female athletes are limited. In the current investigation, we aimed to (1) assess the longitudinal pre- to post-season changes in functional MRI (fMRI) of working memory and working memory performance, (2) quantify the association between the pre- to post-season change in fMRI of working memory and the exposure to head impact and working memory performance, and (3) assess whether wearing a neck collar designed to reduce intracranial slosh via mild compression of the jugular veins can ameliorate the changes in fMRI brain activation observed in the female high school athletes who did not wear collars after a full soccer season. A total of 48 female high school soccer athletes (age range: 14.00–17.97 years) were included in the study. These athletes were assigned to the non-collar group ($n=21$) or to the collar group ($n=27$). All athletes underwent MRI at both pre-season and post-season. In each session, a fMRI verbal N-Back task was used to engage working memory. A significant pre- to post-season increase in fMRI blood oxygen level dependent (BOLD) signal was demonstrated when performing the N-back working memory task in the non-collar group but not in the collar group, despite the comparable exposure to head impacts during the season between the two groups. The collar group demonstrated significantly smaller pre- to post-season change in fMRI BOLD signal than the non-collar group, suggesting a potential protective effect from the collar device. Significant correlations were also found between the pre- to post-season increase in fMRI brain activation and the decrease in task accuracy in the non-collar group, indicating an association between the compensatory mechanism in underlying neurophysiology and the alteration in the behavioral outcomes.

Keywords: female soccer athletes; fMRI; head impact; N-Back task; neck collar; working memory

Introduction

SPORTS-RELATED TRAUMATIC BRAIN INJURIES (STBI) have been linked to a variety of neurological sequelae; however, the majority of impacts faced by athletes are subconcussive in nature.¹ A subconcussive impact (SCI) occurs when a rotational or linear force is transmitted to the head, but does not result in a clinical diagnosis

of sTBI.^{1,2} A single SCI likely has minimal effects, but the aggregate of impacts over the course of an athlete's career may have deteriorative neuropsychological consequences.^{3–5} Recent advances in neuroimaging have shown that there are sequelae of season-long SCI exposures, including alterations in both structural and functional integrity.^{3,4,6,7} White matter structural alterations after a season of contact sports is especially concerning in school-age

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children, as this maturational period is vital for white matter organization, axonal diameter growth, and thickening of the myelin sheaths, which allows for motor-skill, cognitive, and emotional development.^{8–10} Functional MRI (fMRI) studies have also revealed significantly abnormal brain activation patterns associated with working memory tasks in patients with TBI.^{11–17} In our recent fMRI study of working memory using N-Back task,⁷ we demonstrated significantly elevated brain activation in male high school football athletes over a single season after exposure to repetitive SCIs. In addition, electroencephalographic data indicate that SCIs result in decreased amplitudes of P3a (attentional orienting) and P3b (attention resource allocation) during oddball tasks, both of which have been used to predict educational performance and academic achievement in school-age children.¹

Athletes participating in contact sports are inherently at greater risk of sustaining multiple SCIs throughout their athletic careers; however, a quantitative association between the risk level and exposure to head impacts has yet to be established. In a recent study examining high school football athletes, Myer and coworkers found that a season long exposure to SCIs resulted in significant decreases in white matter diffusivity in similar areas as those seen in sTBIs.⁶ With an average of 625 head impacts per season, high school football athletes are commonly thought to be the group with the highest risk of brain injury.² Soccer athletes may have fewer head impacts per season than football players, but they may experience higher order magnitudes of cranial acceleration/deceleration during noninjurious impacts than football athletes.¹⁸ Whereas most head impacts in football are incidental, soccer actively teaches and encourages athletes to use their unprotected head to direct the ball during play in the form of “heading.”^{19,20} During games, ball speeds can reach up to 80 km/h (or 50 mph), with athletes experiencing an average of 6–12 heading impacts per game (median of 432 per year).²⁰ In addition to “in-game” headers, practice sessions sometimes include “heading” drills in which athletes repeatedly field low speed head-balls thrown by teammates and coaches for up to 30 repetitions in close succession.²⁰

Although soccer players purposefully and frequently put themselves in jeopardy of SCIs and even sTBIs, there is a scarcity of devices available to mitigate the risk. Unlike football, in which athletes are required to wear hard-shelled helmets that partially attenuate impact forces, soccer athletes are not allowed to wear such equipment. Padded head gear represents one protective device available for soccer players, but it has demonstrated a limited ability to attenuate forces sustained during low-level head impacts, such as those experienced while heading, or to attenuate brain damage.^{21–23} Although unable to effectively reduce low-level forces imparted to the head, head gear has shown to decrease impact acceleration on the head from a hit with high-speed, high-pressure balls.²¹ Other protective strategies have focused on neck strength training, but with limited success to effectively diminish accelerations caused by heading SCIs.²⁴

The lack of measureable protection afforded by devices that are currently available may be because of their inability to diffuse force and minimize the collision of the brain against the inside of the skull from external accelerations, called “slosh.”²⁵ Instead of attempting to alter existing equipment (that was never meant to counter the “slosh” effect), it is more sensible to implement equipment specifically designed to limit the slosh effects of repetitive SCIs. For this reason, a specialized neck collar was developed to apply gentle bilateral jugular vein compression, promoting mild cerebral engorgement that may reduce intracranial impact energy absorption (during collision) and dampen the effects of SCIs on white matter integrity.

This collar device has shown positive effects in preserving structural and functional integrity in previous prospective neuroimaging studies after half to one season-long uses in football and hockey athletes.^{6,7,26} To our knowledge, the collar has yet to be investigated in females or in any non-helmet-wearing collision or contact sports. The present study aims to (1) assess the longitudinal pre- to post-season changes in fMRI activation and working memory performance, (2) quantify the association between the pre- to post-season change in fMRI working memory brain activation and the exposure to head impact and the working memory performance, and (3) assess whether wearing the collar can ameliorate negative brain activity and memory performance changes observed in the non-collar group after a full soccer season. Corresponding working hypotheses are: there will be a significant pre- to post-season increase in fMRI brain activation during the performance of working memory task in the female athletes in the non-collar group; there will be significant correlations between the pre- to post-season change in fMRI working memory brain activation and the exposure to head impact and between the pre- to post-season increase in fMRI brain activation and the working memory performance; collar wearing will significantly reduce the pre- to post-season fMRI brain activation change compared with non-collar-wearing.

Methods

Participants

The present study was based on a prospective longitudinal pre- to post-season study design that initially recruited a total of 75 female athletes from two local high school soccer teams, 72 of which consented for participation and were enrolled. Fifteen athletes were unable to complete imaging because of metal orthodontics, resulting in 57 participants for imaging collection, which were divided into either a non-collar group ($n=25$) or a group that wore a neck collar device ($n=32$) for the entirety of the soccer season. The entire team of one school (school A) was assigned to the non-collar group, whereas the majority of another school's team (school B) was assigned to the collar group. In order to balance the two groups' sizes, the last seven athletes recruited from school B were divided among the two groups, resulting in four of the seven athletes from school B being assigned to the non-collar group and three of the seven athletes being assigned to the collar group. All 25 participants in the non-collar group completed pre-season MRI. Among these 25 participants, three participants (all from school A) were lost for the following reasons: quitting the team (1), dropping out because of injury (1), and experiencing an early season-ending anterior cruciate ligament (ACL) injury (1). One additional participant from the non-collar group (from school B) was excluded because of the excessive error rate (40%) during the N-Back task performance. These four athletes were excluded from data analysis. All 32 participants assigned to the collar group completed MRI at pre-season. Among these, five participants were lost for the following reasons: being cut from the team (4) and not completing the post-season testing (1). Therefore, a total of 48 high school female athletes, with 21 in the non-collar group and 27 in the collar group, were included in the final analysis. Among these athletes, two from the non-collar group and four from the collar group reported a history of concussion within 5 years prior to the current soccer season.

Impact surveillance and quantification

Each participant was provided with an X-Patch sensor (X2 Biosystems; Seattle, WA).²⁷ The X-Patch is a small and durable device attached by an adhesive patch to the mastoid (behind the ear) that tracks impacts and stores data until it can be uploaded to a PC.

It is composed of a triaxial accelerometer and gyroscope, which measures three axes of linear acceleration and three axes of angular velocity, respectively, to calculate forces imparted to the head and, thus, head impact magnitude. Members of the research staff applied the X-Patch to each participant immediately preceding a practice or game and removed it afterward, and each sensor's recorded data were uploaded to a PC after each exposure. Head impacts were recorded for all games and practices during the soccer season.

N-Back working memory fMRI paradigm and task performance

All participants performed a verbal working memory N-Back task at both the pre- and post-season fMRI sessions. The N-Back task was conducted for 0-Back and 2-Back conditions. The details of the fMRI experimental paradigm have been described elsewhere.⁷ Briefly, the fMRI paradigm used in the present study consisted of five cycles of fixation (12 sec), 0-Back (26 sec), and 2-Back (26 sec) periods. During the 0-Back period, a series of letters, including A, B, C, D, and O, were presented successively in a random order. Participants were instructed to press a handheld button when the letter "O" was presented. During the 2-Back task period, a series of letters, including A, B, C, and D, were presented successively in a random order. Participants were instructed to press a button when a letter shown was the same as the letter that had been presented two trials back. For both the 0-Back and the 2-Back conditions, 80 trials were included (16 per period). Number of targets was 20 for the 0-Back condition and 21 for the 2-Back condition. The stream of stimulus was generated in a random order for the study but remained constant across participants.

N-Back task performance outcome variables included accuracy and response time at both pre- and post-season fMRI sessions.

1. Accuracy was calculated based on Donaldson's nonparametric discrimination score A'^{28} for both the 0-Back task and the 2-Back task responses. The formula for calculating A' is as follows:

$$A' = 0.5 + (\text{hits} - \text{false alarm}) \times (1 + \text{hit} - \text{false alarm}) / [4 \times \text{hit} \times (1 - \text{false alarm})]$$

The score ranges from 0.5 to 1, with a value closer to 1 indicating better accuracy.

2. Response time was calculated as the time between the beginning of letter display and the time when the button was pressed, for both the 0-Back and 2-Back tasks. Only the trials with correct responses were included for calculating this variable.

Description of the neck collar

Participants in the collar group wore a neck collar device that applied mild jugular vein compression with the aim of ameliorating potential slosh injury.²⁹ The collar device was made of an outer collar that consisted of a thermoplastic elastomer (durometer 80 Shore A), an inner collar that consisted of thermoplastic elastomer (durometer 50 Shore A), and a stainless memory steel composite insert. The collar size was determined individually based on neck circumference and the visual evidence of ultrasound internal jugular vein (IJV) dilation. At the initial fitting of the collar, a registered vascular technologist (J.A.) utilized ultrasound to ensure that the proper collar and IJV responses (e.g., visual evidence of IJV dilation superior to collar) occurred as prescribed. Through the support of daily onsite staffing and tracking, the collar group had a compliance rate of 100% through the course of the soccer season for all games and practices.

MRI image acquisition

MR images were all acquired on a 3T Phillips Ingenia scanner (Philips Medical Systems, Best, the Netherlands) with a 32 channel, phase array head coil. A single shot EPI sequence was used for fMRI data acquisition with the following specifications: repetition time (TR)/echo time (TE) = 2000/35 msec; flip angle = 90 degrees; 160 dynamic scans; field of view (FOV) = 240 × 240 mm; image acquisition and reconstruction matrix = 64 × 64; 38 axial slices; resolution = 3.75 × 3.75 × 5 mm. A magnetization-prepared rapid gradient-echo (MP-RAGE) sequence was used to acquire high resolution three-dimensional (3D) T1-weighted images (sagittal): TR/TE = 8.1/3.7 msec; FOV = 256 × 256 mm; matrix = 256 × 256; in-plane resolution = 1 × 1 mm; slice thickness = 1 mm; number of slices = 180. MRI data using additional sequences, including diffusion tensor imaging (DTI), resting state fMRI, and task-based lower extremity motor fMRI, were also acquired. The findings based on these additional sequences will be reported separately.

Image data processing and analysis

Analysis of fMRI working memory data was performed using the FMRIB Software Library (FSL) (www.fmrib.ox.ac.uk/fsl) and Analysis of Functional Neuroimages (AFNI) software packages. The first level fMRI data processing pipeline included reorientation, brain extraction, slice timing correction, alignment, outlying frame identification, and normalization to Montréal Neurological Institute (MNI) 152 template. Motion artifacts in fMRI data were regressed out of using a 24 parameter motion model along with an additional parameter for each outlying volume.³⁰ The residuals from the motion regression were then bandpass filtered from 0.01 to 0.1 Hz and smoothed with a 6 mm (full width at half maximum [FWHM]) Gaussian filter using AFNI's *3dBandpass*. FSL's mixed effect model (FMRIB's Local Analysis of Mixed Effects [FLAME]) was used to generate the 2-Back versus 0-Back contrasts based on the timing of the N-Back paradigm.

The second level analysis included generating the group activation map for the N-back task, testing the pre- to post-season change in the brain activation, and testing the group difference of the longitudinal change, as well as correlation analysis with working memory performance and head impact exposure. The group activation map for the 2-Back versus 0-Back contrast across all 48 participants at pre-season was calculated using FSL's FLAME mixed effect model (model 1) based on the contrast and variance images from individual subjects. The threshold-free cluster enhancement (TFCE) was used with 5000 permutations to account for the potential type I error resulting from the multiple comparisons in the voxelwise data analysis.³¹ The within-group longitudinal fMRI changes between pre- and post-season sessions and the group difference of this longitudinal change were also processed and analyzed in FSL using FLAME with multiple comparisons corrected (TFCE with 5000 permutation). As time of day may potentially affect BOLD response in fMRI, we compared the time when N-Back fMRI started during the day between the two groups. No significant group difference in time of day was found at either pre-season or post-season ($p > 0.05$, two tailed two sample t test). There was no systemic bias as to whether the post-season scan was done earlier or later in the day than the pre-season scan in either of the two study groups ($p > 0.05$, two tailed paired t test). In addition, we also examined head motion data to rule out their potential confounding effect on the findings. The x, y, z rotation and translation parameters (in radian and mm, respectively) derived from the frame-by-frame realignment, as well as the root mean square motion and frame-wise displacement (both measured at a 50 mm radius), were first compared between the two groups at both pre- and post-season time points and then tested longitudinally for pre- to post-season difference. No statistically significant findings were identified in any of these comparisons (all $p > 0.05$, two tailed, two sample t test in cross-sectional comparisons between groups;

paired *t* test in longitudinal comparisons between time points). Detailed statistical results from these comparisons can be found in Tables S1–S3 (see online supplementary material at <http://www.liebertpub.com>). Several additional variables, including age, the time intervals between the pre- to post-season scanning and between the last head impact and post-season, as well as the head impact exposure variables at different *g* force thresholds, were also individually tested as covariates for potential confounding effects in the analysis of group differences of longitudinal activation change. As none of these variables showed significant effects during the initial test, they were not included in the final statistical analysis.

In the correlation analysis, we first calculated the difference in the pre- and post-season Z maps from the brain areas that presented significant longitudinal within-group difference in fMRI brain activations. The Automated Anatomical Labeling (AAL) atlas was used to parcellate brain regions with significant longitudinal change into individual anatomical regions. The pre- to post-season difference in Z-statistics was extracted from these individual segments and used for correlation with change in task performance and exposure to head impacts based on Pearson correlation analysis.

Results

Participants characteristics

The ages of the 48 female high school athletes who were included in the final analyses ranged from 14.00 to 17.97 years (median, 15.98; mean $\pm$ SD, 16.03 $\pm$ 1.08 years) at pre-season. No statistically significant age difference was found between these 48 participants and the 9 participants excluded from this analysis (median, 15.77 years; mean $\pm$ SD, 15.86 $\pm$ 0.72 years; range, 14.83–

16.86 years). Among the 48 participants who were included in the final analyses, no significant group difference in age at pre-season imaging was noted (non-collar group, 15.99 $\pm$ 1.04 years; collar group, 16.06 $\pm$ 1.13 yrs). Detailed descriptive statistics of age (median, mean, standard deviation, and range) can be found in Table 1.

The time interval between the pre- and post-season scan ranged from 59 to 118 days. The time between the last head impact and the post-season scan ranged from 0 to 20 days. No statistically significant difference was found between the two study groups in either of these two time interval variables (Table 1).

Exposure to the repetitive head impacts during the season

The head impact exposure variables, including the total number of head impacts, the average *g* force/hit, and the cumulative *g* force experienced during the season at different *g* force thresholds are presented in Table 1. No statistically significant difference was found in any of the group comparisons.

fMRI N-Back task performance

The descriptive statistics of fMRI task performance, including both 0-Back and 2-Back, are included in Table 2. The two study groups were comparable in task performance, accuracy, and response time (in N-Back tasks) in both fMRI sessions. No significant pre- to post-season changes were found for N-Back accuracy or response time (Table 2).

TABLE 1. DEMOGRAPHIC INFORMATION OF PARTICIPANTS, TIMING OF IMAGING, AND EXPOSURE TO HEAD IMPACT

	Non-Collar (n=21)				Collar (n=27)				Statistics	
	Median	Mean	SD	Range	Median	Mean	SD	Range	t	p
Age (years)	15.99	15.99	1.04	14.42–17.76	16.00	16.06	1.13	14.00	0.24	0.81
Gender	All female				All female					
Ethnicity										
Time (days, pre- to post-season MRI)	91	91.19	17.26	59–118	97	95.15	12.02	66–113	0.94	0.35
Time (days, last impact to post-season MRI)	1	2.52	4.33	0–20	2	4.07	5.11	0–17	1.11	0.27
Number of hits										
all	838	867	457	251–2057	824	897	378	358–2001	0.24	0.81
>15g	194	272	153	76–564	241	260	93.0	129–487	0.32	0.75
>20g	123	163	93.5	45–404	139	157	58.9	78–327	0.24	0.81
>50 g	22	26.3	16.3	3–58	25	25.3	8.94	12–53	0.26	0.80
>100g	2	3.33	2.65	0–9	3	3.26	1.81	0–8	0.11	0.91
Cumulative g force										
all	11566	14107	7362	4294–29836	13080	13810	4631	5909–23485	0.17	0.87
>15g	5753	7808	4321	2237–17084	6950	7537	2509	3794–14665	0.27	0.79
>20g	4613	5938	3377	1718–14335	5238	5764	1991	2882–11901	0.22	0.82
>50g	1545	1932	1158	274–3981	1852	1896	665	737–3780	0.13	0.89
>100g	244	421	339	0–1090	403	400	230	0–1028	0.25	0.80
Average g force/hit										
all	16.01	16.31	1.54	12.92–19.50	16.16	15.85	1.73	11.74–19.28	0.95	0.34
>15g	29.24	28.86	2.36	23.37–33.09	29.23	29.21	2.16	25.17–34.03	0.53	0.60
>20g	37.24	36.49	2.51	31.40–40.25	36.60	36.95	2.55	30.90–42.20	0.63	0.53
>50g	74.25	74.78	6.56	66.10–91.18	74.35	74.78	6.05	61.44–91.82	0.00	1.00
>100g	121.09	126.49	14.12	103.5–152.2	122.95	122.50	12.45	100.7–166.8	0.99	0.33

TABLE 2. fMRI N-BACK TASK PERFORMANCE

	Pre-season				Post-season				Statistics	
	Median	Mean	SD	Range	Median	Mean	SD	Range	t	p
0-Back, non-collar, <i>n</i> = 21										
Accuracy (A')	0.988	0.987	0.005	0.975–1.000	0.988	0.984	0.014	0.925–1.000	0.84	0.41
Response Time (msec)	452.0	465.8	50.65	367.9–586.1	470.5	476.0	66.2	386.1–622.9	0.86	0.40
0-Back, collar, <i>n</i> = 27										
Accuracy (A')	0.988	0.989	0.006	0.975–1.000	0.988	0.988	0.008	0.965–1.000	0.54	0.59
Response Time (msec)	474.8	473.7	54.6	368.7–588.0	458.4	460.5	52.4	367.6–588.0	1.39	0.18
2-Back, non-collar, <i>n</i> = 21										
Accuracy (A')	0.976	0.966	0.030	0.905–1.000	0.976	0.974	0.020	0.934–1.000	1.20	0.24
Response Time (msec)	508.3	523.1	96.0	375.8–713.9	508.1	511.5	68.2	390.7–612.7	0.84	0.41
2-Back, collar, <i>n</i> = 27										
Accuracy (A')	0.976	0.968	0.030	0.887–1.000	0.976	0.965	0.033	0.853–1.000	0.43	0.67
Response Time (msec)	498.3	520.1	87.6	366.3–754.3	469.6	504.9	115.1	352.6–846.5	0.79	0.44

Accuracy was calculated based on Donaldson’s nonparametric discrimination score A’. The score ranges from 0.5 to 1, with a value closer to 1 indicating better accuracy

fMRI brain activation of N-Back working memory

Figure 1 presents the brain regions where the fMRI BOLD signal was significantly higher during the performance of the N-Back tasks (composite Z-score map, 2-Back >0 Back) in the entire cohort (*n* = 48, including participants from both groups) at the pre-season fMRI session. Significant activation was defined as *p* < 0.05 after correction for multiple comparisons based on permutation (TFCE approach) testing. During the pre-season assessment, significant activation differences (increased BOLD signal during 2-Back when compared with 0-back) were found in a series of bilateral or unilateral

anatomical loci including the cingulate gyrus, dorsolateral and ventrolateral prefrontal cortex, lateral and medial premotor cortex, medial posterior parietal lobe, inferior parietal lobe, cingulate gyrus, thalamus, and cerebellum (Fig. 1). No significant differences in fMRI BOLD signal at pre-season were found between the 21 participants in the non-collar group and the 27 participants in the collar group.

Composite Z-score map based on 2-Back <0 Back contrast was also calculated and used in the subsequent statistical analyses of the longitudinal pre- to post-season change in the BOLD signal in both study groups. All the results based on the longitudinal analyses of 2-Back <0 Back contrast, however, were negative. Therefore, only

FIG. 1. N-Back working memory brain activation in all 48 female soccer athletes at pre-season (Z-score >3, *p* < 0.005, corrected). The Z-score value in the upper left corner in all the panels represents the z coordinate in mm. Color image is available online at www.liebertpub.com/neu

the results based on the 2-Back >0-Back contrast will be reported in the subsequent sections.

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

Figure 2 presents the composite p value map for brain regions within the non-collar group that showed significantly stronger activation ($p < 0.05$, TFCE corrected) for the 2-Back >0-Back contrast at post-season when compared with pre-season. The anatomical regions based on the AAL atlas, the coordinates, and the volumes of these anatomical loci are reported in Table 3. No brain region was found to show significantly lower activation at post-season than at pre-season in the non-collar group.

No significant longitudinal change between pre- and post-season was found in either direction in the collar group.

Group difference of longitudinal change in N-Back working memory brain activation

Significantly larger pre- to post-season changes in brain activation were found in the non-collar group than in the collar group ($p < 0.05$, TFCE corrected). Figure 3 presents the composite p value map that shows areas of the brain with significant increase in activation after the season (in the non-collar group) using the longitudinal change in activation 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 specific brain regions (based on AAL atlas) with significant group difference (as shown in Fig. 3), the centroid coordinate, and

the volume of these regions, are reported in Table 4. No region was found to have significantly greater pre- to post-season change in the collar group than that in the non-collar group.

Association between the longitudinal change in brain activation and exposure to head impact

No significant correlation was found between the change in N-Back working memory brain activation, and the head impact exposure variables (including total number of hits, average g force/hit, and cumulative g force at different g force thresholds) in either of the two study groups.

Association between the longitudinal change in brain activation and change in task performance

In the non-collar group, significant correlation was found between the pre- to post-season change in fMRI activation in a series of brain regions (including left inferior frontal gyrus, opercular gyrus, left inferior gyrus, triangular gyrus, right inferior parietal lobe, and bilateral angular gyrus) and the change in N-Back task accuracy (Table 5). As shown in Figure 4, in the non-collar group, the longitudinal increase in fMRI signal in the pars triangularis of the left inferior frontal gyrus was positively correlated to the decrease in task accuracy in the 21 athletes in the non-collar group.

No significant correlation was found between the longitudinal change in fMRI activation (in any brain regions of interest) and the change in response time in the non-collar group. In the collar group, no significant correlation was found among the longitudinal change in fMRI activation (in any brain regions of interest), change in response time, or the change in accuracy.

FIG. 2. Brain regions with statistically significant pre- to post-season difference (post > pre) in N-Back working memory brain activation in the non-collar group (Z -score > 3 , $p < 0.05$, corrected). The z value in the upper left corner in all the panels represents the z coordinate in mm. Color image is available online at www.liebertpub.com/neu

TABLE 3. MNI COORDINATES AND VOLUMES OF THE BRAIN REGIONS THAT PRESENTED STATISTICALLY SIGNIFICANT PRE- TO POST-SEASON INCREASE OF THE fMRI BOLD SIGNAL IN THE N-BACK WORKING MEMORY TASK (2-BACK > 0-BACK CONTRAST) IN THE NON-COLLAR GROUP

Anatomical regions	Volume (voxels)	MNI Coordinate		
		x	y	z
L. precentral gyrus	514	-46.5	5.4	38.8
L. superior frontal gyrus	316	-17.9	10.7	54.6
L. middle frontal gyrus	603	-30.2	9.5	53.0
L. inferior frontal gyrus (pars opercularis)	254	-45.3	10.5	22.8
L. inferior frontal gyrus (pars triangularis)	448	-43.0	23.6	20.7
L. supplemental motor area	379	-4.2	13.5	52.6
R. supplemental motor area	80	4.6	16.3	50.8
L. superior medial frontal gyrus	147	-3.8	23.9	41.4
R. superior medial frontal gyrus	56	6.6	24.8	43.9
L. insula	22	-30.8	21.7	11.5
L. anterior cingulum	29	-7.8	21.2	28.5
L. middle cingulum	85	-6.7	21.6	34.9
R. middle cingulum	106	6.9	22.3	37.5
L. superior occipital lobe	95	-22.7	-71.6	34.6
R. superior occipital lobe	64	31.2	-69.5	42.6
L. middle occipital lobe	271	-27.4	-69.4	34.3
R. middle occipital lobe	92	34.0	-67.7	34.5
L. post-central gyrus	131	-37.6	-38.7	50.9
R. post-central gyrus	100	36.3	-42.1	58.9
L. superior parietal lobe	1080	-25.4	-60.5	55.2
R. superior parietal lobe	1123	25.8	-59.9	60.1
L. inferior parietal lobe	1194	-37.7	-48.3	47.4
R. inferior parietal lobe	257	35.3	-47.5	49.5
L. supramarginal gyrus	3	-44.0	-38.7	34.0
R. supramarginal gyrus	71	39.4	-38.1	40.1
L. angular gyrus	11	-32.9	-59.8	37.5
R. angular gyrus	264	33.9	-62.5	44.9
L. precuneus	644	-7.6	-65.0	53.0
R. precuneus	545	8.0	-62.6	55.3

MNI, montréal neurological institute; fMRI, functional MRI; BOLD, blood oxygen level dependent.

Discussion

Sports and recreational activities contribute to ~21% of all TBIs among American children and adolescents.³² As such, the role of cumulative head trauma on functional or behavioral measurement changes across time has received increasingly more attention.³³ In addition, high school athletes are in the midst of a critical neurodevelopmental period.³⁴ Up to this point, there have been few neuroimaging studies investigating acute or residual effects of SCI in soccer.³⁵ Therefore, we focused on a cohort of high school female athletes to further examine the possible neurological sequelae of a season of soccer participation.

Prior research into the pathophysiology of cumulative head impact in sports has identified both structural and functional changes associated with repetitive head impacts in a single season of football.^{3,6,7} However, research within non-helmeted sports and female populations has yet to appear as prevalent in existing literature as football. The head impact exposures recorded from the female soccer athletes in the current study (Table 1) are indeed lower than the male football athletes at a comparable age range and

level of competition.^{6,7,36,37} Recent studies have reported a higher false positive rate in studies using the X-Patch than the GForce Tracker sensors,^{38,39} which suggested an even relative lower level of exposure to head impact in the present study in comparison with the male football studies.^{3,6,7} Despite this, we still found significant alterations in brain activation in several brain areas during working memory tasks in our non-helmeted cohort, and after only one season (Fig. 2). Further, in the non-collar group, significant correlations were found between the pre- to post-season changes in fMRI activation in a series of brain regions, including left inferior frontal gyrus (pars opercularis and pars triangularis), right superior medial frontal gyrus, right superior occipital lobe, left superior parietal lobe, right inferior parietal lobe, and bilateral angular gyrus, and the N-Back task accuracy (Table 5). These results are in line with prior literature, and add new support about the engagement of the frontoparietal network and the cingulo-opercular network in working memory and their vulnerability under insults.^{17,33,40–43}

fMRI of working memory using the N-Back task has been applied frequently in studying the functional integrity of the brain network in patients with TBI across a spectrum of different injury levels.^{11,12,14–17,44–48} In all these studies (including participants with TBI, concussion, or SCIs), significant findings based on fMRI N-Back for working memory occurred most commonly in the dorsolateral and ventrolateral prefrontal cortex, the supplementary motor and premotor areas, and the posterior parietal area (which are known to be associated with working memory, spatial processing, attention, and executive function). Although some studies have shown weaker BOLD signal in response to working memory tasks in TBI patients than in controls,^{16,17,49,50} the literature generally supports that there is an increase in brain activity after TBI. For example, in the seminal experiments by McAllister and coworkers in 1999 and later in 2001,^{11,12} there was a stronger BOLD signal in the 2-Back versus 1-Back contrast in adult patients with mild TBI at 1 month post-injury than in controls. A more recent study of TBI by Smits and coworkers⁴⁶ also showed hyperactivation in adult TBI patients with moderate to severe post-concussive symptoms, with the elevated activation level strongly associated with severity level. Newsome and coworkers conducted a longitudinal fMRI study of adult patients with moderate to severe TBI started from 3 to 18 months after injury.⁴⁵ Although the fMRI activations were comparable at baseline, the patients in the group with pharmacological treatment exhibited a significant reduction in brain activation in comparison with the patients in the placebo group.⁴⁵ Wylie and coworkers⁴⁸ used fMRI to compare patients with mild TBI at two different time points: 3 days versus 1 week post-injury. In their study, a longitudinal increase in brain activation was found in the subset of patients whose cognitive function was impaired and remained unchanged at both acute and subacute time points, whereas no change in brain activation was identified in patients whose cognitive function recovered to normal level at the follow-up.

Recently, there has been growing literature applying N-Back fMRI experiments in studying the potential deficits in working memory among contact sport athletes with concussion^{51–54} and athletes exposed to repetitive SCIs.^{7,55–58} In youth and young adult athletes with sports-related concussion, patients with concussion were found to have elevated brain activation compared with the controls.^{51–54} The abnormally elevated activation was found to be associated with self-reported concussion symptom severity.⁵² The difference in patient versus control brain activation was found to have diminished after recovery,⁵³ or be associated with the length of clinical recovery.⁵¹ In our recent fMRI study,⁷ with a similar pre- to post-season longitudinal study design as that in the present study,

FIG. 3. Brain regions with greater pre- to post-season increase in activation in the non-collar group ($n=21$) than in the collar group ($n=27$, $p<0.05$, corrected). The z value in the upper left corner in all the panels represents the z coordinate in mm. Color image is available online at www.liebertpub.com/neu

we investigated the change in brain activation in high school football athletes after a single season with accelerometer quantification of SCIs. BOLD signal changes were significantly elevated in the non-collar football athletes when tested at post-season in comparison with pre-season, and the head impact exposure was significantly correlated with this pre- to post-season increase in brain activation. In the present female soccer study, as described earlier, despite lower head impact exposures than the football athletes, significant elevation in brain activation in response to the N-Back task was found at post-season testing in the non-collar group (Table 3), similar to the findings in the above-described reports. This elevated brain activation can be interpreted either as a brain response to recruit additional neural resources to compensate for transiently impaired neuronal functions (the compensation theory), or as a change that involves more permanent alterations in structural and/or functional networks (reorganization theory).^{11,12,59,60} Unlike the fMRI study of working memory in football athletes,⁷ no significant correlation was found in the present study between the head impact exposure and the changes in brain activation. In the non-collar group in the present study, elevated brain activation occurred across the spectrum of hits and force. It is unclear whether the absence of a correlation between head impacts and brain activity change can be attributed to the smaller range of head impact measures (intensity and frequency), the potential ceiling effect perhaps being the result of a female advantage in verbal working memory and the potential confounding effects on working memory performance and brain activity,⁶¹ tighter range in task performance, the different profile in the head contact between sports, or other differences in baseline characteristics.^{7,62,63}

Despite these issues, the present study lends further credence to previously published neurofunctional data⁶⁴ and further attempts to

correlate fMRI findings with actual functional deficits. Specifically, we identified a series of brain regions in which there was a significant correlation between the increase in brain activation and change in N-Back response accuracy in the non-collar athletes. These regions include the pars opercularis in left inferior frontal gyrus (BA44, involving semantic and executive functions), the pars triangularis in the left inferior frontal gyrus, the right inferior parietal lobe, and the bilateral angular gyrus (comprehension of visually perceived words, language, spatial cognition, memory retrieval, and attention) (Table 5). If we adopt the compensation mechanism as described, the brain regions in a participant who had better task accuracy at post-season would need to increase neuronal activity to accommodate the demand from the increase performance in that individual. It should be noted that the non-collar group did not present significant longitudinal pre- to post-season group-wise change in the task performance, and it is not uncommon to observe comparable performance along with significant difference in the BOLD signal in response to the task.^{11,12,15,48,53,54} The sustained performance in our case from pre- to post-season could be the result of the SCI nature of the exposure because, by their nature, repetitive SCIs induce little acute behavioral or memory performance changes; however, they may start a neurological cascade predisposing the individual to long-term or chronic behavioral declines. It is premature to conclude that neuroimaging results based on fMRI are more sensitive than behavioral performance outcome measures. Lower fMRI task performance in patients has often been reported to be load dependent;^{65,66} that is, the difference sometimes does not manifest unless participants with cognitive deficits are fully challenged to the limit of their capacity. The relationship between the task performance and BOLD signal remains to be further investigated at different task load levels.

TABLE 4. MNI COORDINATES AND VOLUMES OF THE BRAIN REGIONS THAT PRESENTED STATISTICALLY SIGNIFICANT GROUP (NON-COLLAR > COLLAR) DIFFERENCE IN THE PRE- TO POST-SEASON INCREASE OF THE fMRI BOLD SIGNAL IN THE N-BACK WORKING MEMORY TASK (2-BACK > 0-BACK CONTRAST)

Anatomical regions	Volume (voxels)	MNI Coordinate		
		x(mm)	y(mm)	z(mm)
L. precentral gyrus	264	-30.2	0.4	45.6
L. superior frontal gyrus	185	-16.7	9.2	54.9
L. middle frontal gyrus	138	-25.1	6.3	51.1
L. supplemental motor area	186	-4.6	13.1	51.7
R. supplemental motor area	37	3.8	14.6	50.5
L. superior medial frontal gyrus	42	-5.8	19.9	41.5
R. superior medial frontal gyrus	13	6.0	21.7	43.1
L. anterior cingulum	17	-7.2	21.2	28.6
L. middle cingulum	50	-8.0	21.1	34.8
R. middle cingulum	9	8.0	21.1	40.4
L. superior occipital lobe	60	-21.5	-70.2	36.3
R. superior occipital lobe	63	30.1	-68.5	42.5
L. middle occipital lobe	124	-26.3	-66.7	34.6
R. middle occipital lobe	33	32.0	-66.2	34.8
L. post-central gyrus	50	-30.8	-42.3	51.9
R. post-central gyrus	51	33.9	-45.5	63.6
L. superior parietal lobe	628	-24.0	-59.7	54.4
R. superior parietal lobe	831	24.2	-61.1	60.4
L. inferior parietal lobe	830	-38.7	-46.4	47.1
R. inferior parietal lobe	140	34.8	-46.7	50.4
L. supramarginal gyrus	1	-44.0	-42.0	34.0
R. supramarginal gyrus	31	35.1	-38.2	43.2
R. angular gyrus	103	31.7	-62.9	46.9
L. precuneus	488	-8.3	-64.3	54.8
R. precuneus	337	9.0	-59.2	59.1

MNI, montréal neurological institute; fMRI, functional MRI; BOLD, blood oxygen level dependent.

The current investigation highlights encouraging preservation of working memory capacity in females wearing the collar during a season of high school soccer. In a prior neuroimaging study,⁶⁷ athletes participating in high-frequency heading resulted in lower fractional anisotropy measures using DTI in the temporo-occipital white matter as well as worse performance in memory tasks than those participating in lower-frequency heading. Although this prior

TABLE 5. SIGNIFICANT CORRELATIONS BETWEEN PRE- TO POST-SEASON fMRI ACTIVATION CHANGE IN DIFFERENT BRAIN REGION IN THE NON-COLLAR GROUP (N=21) AND CHANGE IN N-BACK ACCURACY

Anatomical regions	r	p
L. inferior frontal gyrus (pars opercularis)	0.568	0.0072
L. inferior frontal gyrus (pars triangularis)	0.639	0.0018
R. superior medial frontal gyrus	0.451	0.0403
R. superior occipital lobe	0.465	0.0339
L. superior parietal lobe	0.442	0.0449
R. inferior parietal lobe	0.480	0.0276
L. angular gyrus	0.438	0.0470
R. angular gyrus	0.508	0.0187

fMRI, functional MRI.

FIG. 4. Correlation between pre- to post-season change in blood oxygen level dependent (BOLD) activation and the change in the 2-Back task performance. A' is the task accuracy based on the Donaldson's non-parametric discrimination score. Color image is available online at www.liebertpub.com/neu

investigation adds valuable insight to existing literature, it investigated primarily male athletes, making comparisons with our study difficult to ascertain. Further, the cross-sectional study design and the use of a questionnaire in quantifying heading frequency in this prior study limited the ability to objectively identify the effect of repetitive head trauma on brain structure. Past research has found that female athletes demonstrate a higher risk of head injury than male athletes.⁶⁸⁻⁷¹ This has been attributed to various anatomical and biomechanical differences such as females having relatively less head to neck-segment stiffness and strength than males, and the potential confounding element of monthly hormonal changes to the cerebral vascular tree. These differences may make females less effective at dampening the magnitude of the head's kinetic response to impact and puts them at greater risk during contact sports.⁷²⁻⁷⁴ Therefore, the current investigation will help fill the knowledge gap about potential brain injury in female athletes, who have not been studied as thoroughly as their male counterparts. It will benefit females by providing a mechanism to reduce the impact of SCI on neurological function that circumvents classic approaches such as helmet design, and may mitigate sex-related increased risk.

Limitations

Several limitations should be considered when assessing this study. The authors acknowledge that a potential "ceiling effect" may be present in performing just a 2-Back fMRI working memory task (one that is not only simple but may be learned and improved upon with repetition). The female advantage in verbal working memory has been reported in previous fMRI studies⁶¹ and was also reflected in the task accuracy in the present study when compared with a recent fMRI study in male football athletes (comparing Table 2 in the present study and Table 2 in the article by Yuan and coworkers⁷). This may be attributable to gender difference in structural and cognitive domains as previously reported in the literature.^{62,63} Increasing intellectual complexity or load should be considered in future studies. In the present study, the change in BOLD signal was interpreted primarily as being neural in origin (an indirect index for cognitive change). However, the authors acknowledge that BOLD signal can come from both neural and vascular changes. Even though the vascular factor usually is not a

concern unless the population under study is associated with major vascular abnormalities, as, for example, stroke, the vascular change cannot be ruled out as a contributing factor in the results. Over the course of a season of repetitive head impacts, subtle vascular change may develop and contribute to the longitudinal increase in BOLD signal within the non-collar group as well as in the between-group contrast of BOLD signal change. The relatively small sample size is another potential limiting factor. Although we have tested and excluded the potential confounders (age, time intervals, SCI loads) in the initial analysis, we were underpowered to conduct a rigorous statistical analysis that included all the potential variables. In the present study, the randomization was done at a team level. We did not assign athletes with subject-based randomization primarily because of logistical difficulties. Although the two schools selected were from the same district and were closely matched athletically and in socioeconomic composition, we acknowledge that randomizing within a team would provide an ideal study design if given the required logistical resources to minimize the potential confounding effect. It should be noted that additional issues would arise using within-team randomization, (e.g., player position and potential exposure differences in a team) and will need to be taken into consideration for future study designs. Additional factors, such as menstrual cycle/estrogen level⁶¹ and heading statistics,⁶⁷ may need to be evaluated in future studies. Also, because of the absence of a normal control group, we cannot conclude that the difference between the non-collar group and the collar group was solely attributable to head impacts. Other factors, such as exercise level, could potentially contribute to the differences observed. Including a control group in a non-contact sport but with a comparable amount of exercise in future studies is needed to help confirm the current findings.

Conclusions

Our findings suggest that greater brain activation changes occurred across a season of soccer in a group of female adolescents who were not wearing a protective collar device than in those wearing the collar, despite similar levels of head impacts sustained during the season. We also identified significant correlations between the pre- to post-season increase in fMRI brain activation and the decrease in task accuracy in the non-collar group. The data in the present study suggest that wearing an external jugular vein compression collar may help to preserve working memory abilities among those who are exposed to repetitive head impact during sports.

Acknowledgments

We thank: from Seton High School Ron Quinn, Lisa Larosa, Holly Laiveling, and the entire soccer coaching staff as well as the Seton administration and Athletic Director Wendy Smith; and from Madeira High School Soccer Head Coach Dan Brady, Athletic Director Joe Kimling, and Principal David Kennedy for their support and assistance to conduct this study. We also thank the soccer parents and players for participating and supporting the efforts to complete the project. We appreciate their patience with the testing, scheduling, and follow-up testing. Their enthusiastic support made this study possible. Special acknowledgement goes to the athletic trainers Cindy Busse at Seton High School and Glenna Knapp at Madeira High School. Without their time, commitment, and passion for the health and well-being of their student athletes, this study would not have been possible. We also thank University of Cincinnati interns Casey McCall, Danielle Reddington, Preston Heath, and Jacob Snyder for their assistance with the daily accelerometer tracking. Funding for this study was provided by The

Heidt Family Foundation, Robert S. Heidt, Sr.—Wellington Foundation and Q30 Sports Sciences, LLC. Funding for this study was provided to Cincinnati Children's Hospital Medical Center from Q30 Innovations, LLC.

Author Disclosure Statement

David Smith is the inventor of the Q-Collar approach and has financial interest in the results of the current research. The other authors have nothing to disclose. Gregory D. Myer consults with Q30 Innovations to support applications with the US Food and Drug Administration but has no financial interest in the commercialization of the Q-Collar.

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