CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

STUDY TITLE: Controlled DTI evaluations in High School Football and Female Soccer to evaluate efficacy of jugular compression collar

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INVESTIGATOR INFORMATION:

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(1) ABSTRACT:

Significant morbidity, mortality, and related costs are caused by traumatic brain injury (TBI). A simple, effective, and lightweight device worn by athletes or war fighters in the field, designed to mitigate TBI resulting from blast trauma or concussive events, would save lives, and the huge costs incurred for life-treatment of surviving victims. An externally-worn medical device that applies mild jugular compression according to the principle of the Queckenstedt Maneuver (the Device) is being developed by Q30 Sports Science, LLC (Q30) (Figure 1). Preliminary research indicates that the Device has the potential to reduce the likelihood of alterations to brain microstructure. The currently developed collar has been approved for studies in humans and the results indicate safety for use during high demand and maximal exertion activities, *Study IDs: 2013-2240, 2016-7948, 2014-5009, 2016-9625, 2016-0988, and 2015-2205 Institutional Review Board - Federalwide Assurance #00002988)* (Myer, Yuan et al. 2016, Myer, Yuan et al. 2016, DiCesare, Barber Foss et al. 2017, Yuan, Leach et al. 2017, Yuan, Barber Foss et al. 2018, Yuan, Dudley et al. 2018). FDA has determined that this device is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812).

Figure 1: Collar Device

This study will investigate the effectiveness of this device in high school athletes playing a collision sport such as football or soccer. Athletes participating in this study will be randomly assigned to one of two groups: 1) Device wearing during the season or 2) Non-device wearing during the season. Male football players and female soccer players will be included in this investigation. All participants may be outfitted with an accelerometer which will measure the magnitude of every impact to the head sustained by the athlete. This accelerometer will be affixed with an adhesive patch,(which will be placed behind the ear, to measure the magnitude of every impact to the head sustained by the athlete Effectiveness of the device will be determined via differences in longitudinal brain imaging and behavioral assessments following competitive football and soccer participation. We will also enroll a group of athletes involved in a non-contact sport (such as cross-country) to act as controls.

(2) PURPOSE OF STUDY:

The purpose of the study is to monitor longitudinal changes in brain structure between the preseason and postseason, in a population of football and soccer playing athletes wearing the Device and compared to a similar population not wearing the device. Secondly, the purpose is to determine the efficacy of device to reduce alterations in brain structure relative to amount and magnitude of sustained head impacts. Finally, to show that DTI efficacy and safety results can be prospectively confirmed in a multi-school investigation.

Test the null hypotheses of no difference between collar users and non-collar users changes from baseline to end of season for:

- Primary: Alterations in pre-defined DTI metrics (AD, MD, RD) are significantly reduced in the neck collar group at EOS relative to BL.
- Secondary: Alterations in pre-defined DTI metrics is explained by the number of hits, the hit intensity, and the intensity per head impact over the season non-collar users.

(3) BACKGROUND:

Summary of Prior Work: Pre-Clinical Trials

Prior to the onset of *in vivo* clinical trials, animal studies (rat) of slosh mitigation showed that venous compression in the neck applied during a standardized mild TBI model (Marmarou, Foda et al. 1994) significantly reduced the extent of axonal injury.(Smith, Bailes et al. 2012) Extent of axonal injury was determined by quantification of amyloid precursor protein (APP) immuno-histological staining. **Figure 2** shows the rat device *in situ*, and a summary of the results of this study. In addition, further analysis in the same rat brains showed that established histological biomarkers of TBI (Woodcock and Morganti-Kossmann 2013) were reduced in parallel with slosh mitigation.(Turner, Naser et al. 2012) In this study, we observed a 48.7%–59.1% reduction in degenerative neurons, a 36.8%–45.7% decrease in reactive astrocytes, and a

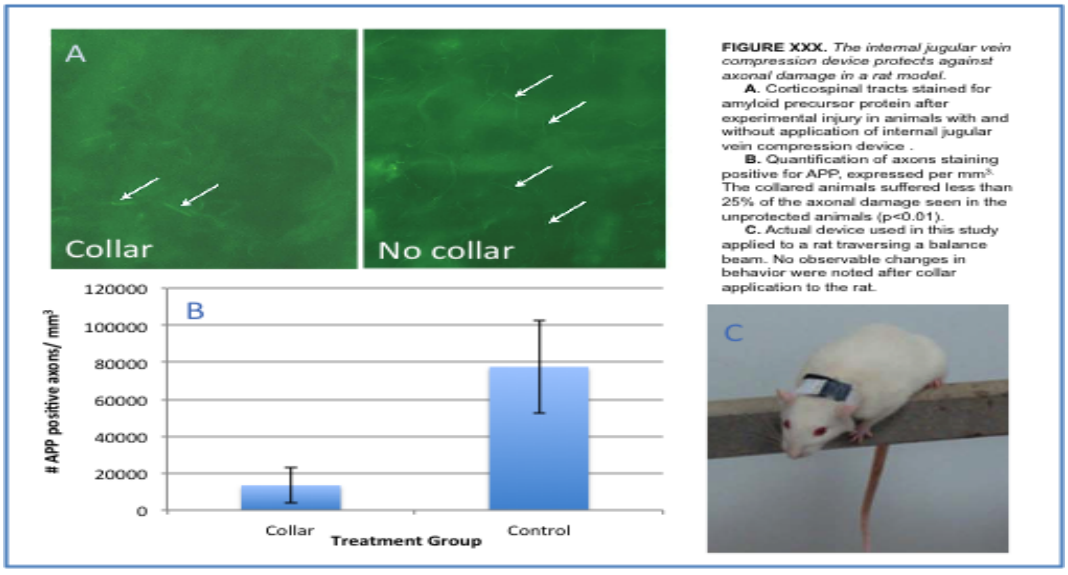


Figure 2. A. Corticolspinal tracts stained for APP after experimental injury. **B.** Quantification of axons staining for positive APP, expressed per mm^3 **C.** Investigational device utilized. No observable changes in behavior were noted following collar application.

44.1%–65.3% reduction in microglial activation, all of which indicate a significant reduction in inflammatory response and neuronal damage after mTBI attributable to jugular vein compression.

At the request of the FDA, an investigation was conducted to alleviate concerns of increasing the propensity for hemorrhage and hemorrhagic propagation with applied jugular vein compression. This study aimed to test the safety of IJV compression in a large animal controlled cortical impact (CCI) injury model and the resultant effects on hemorrhage. Twelve swine were randomized to placement of a bilateral IJV compression collar (CCI+collar) or control/no collar (CCI) prior to CCI injury. A histological grading of the extent of hemorrhage, both subarachnoid (SAH) and intra-parenchymal (IPH), was conducted in a blinded manner by two neuropathologists. Other various measures of TBI histology were also analyzed including: b-amyloid precursor protein (b-APP) expression, presence of degenerating neurons, extent of cerebral edema, and inflammatory infiltrates. Euthanized 5 h after injury, the CCI+collar animals exhibited a significant reduction in total SAH ($p = 0.024–0.026$) and IPH scores ($p = 0.03$-0.05) compared with the CCI animals. There was no statistically significant difference in scoring for the other markers of TBI (b-APP, neuronal degeneration, cerebral edema, or inflammatory infiltration). In conclusion, IJV compression was shown to reduce hemorrhage (SAH and IPH) in the porcine CCI model when applied prior to injury (**Figure 3**). These results suggest the role of IJV compression for mitigation of not only axonal, but also hemorrhagic injury following TBI.

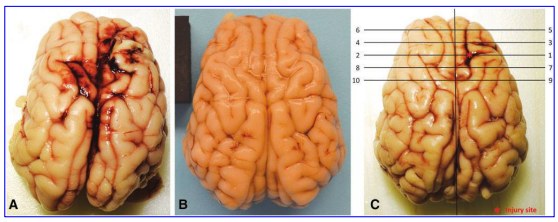


Figure 3. Representative hemorrhage from whole brain gross pathology of (A) controlled cortical impact (CCI) and (B) CCI+collar swine brain. (C) Depiction of anatomical sectioning (10 total plus sections from bilateral thalami) in relation to CCI injury site.

Summary of Prior Work: Clinical Trials

Prior to the initiation of clinical trials, the BIC research team employed a large scale epidemiologic investigation to evaluate a potential mechanism by which brain slosh dynamics can be controlled via physiologies that occur during acclimatization to altitude such as increased diphosphoglycerate, red cell mass, intracranial pressure and volume (the intent was to see if the latter two adaptations, which also occur with the jugular compression device in place, might be protective against TBI). The investigations were approved by the local IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory *(Study ID: Waiver)*. The first study evaluated 5,936 concussions that occurred in 20,618,915 exposures reported by athletic trainers from a large national sample of United States high schools to evaluate the effect of topographical elevation from nearly sea level to nearly 7,000 ft. We hypothesized that in the chronic phases of adaptation at topographical elevation erythropoietin (Epo) will have increased blood synthesis

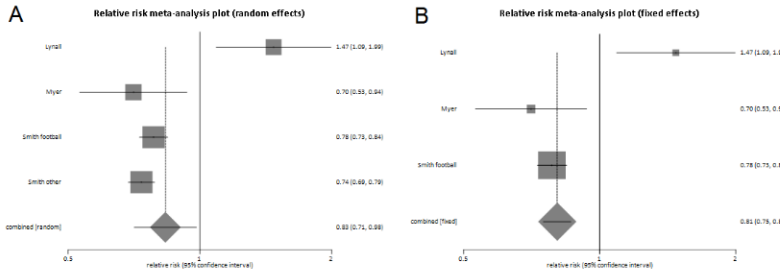


Figure 4 (A) Random-effects model using all available data (4 studies); (B) Fixed-effects model of included American football studies demonstrating the effect of increased altitude on reduced concussion incidence.

leading to relative polycythemia. Our results indicate that the increased topographical elevation may contribute to an internal cranial environment that is protective to the brain against concussion in both practice and competition. Specifically, elevated topographical elevation was associated with a reduction in concussion rates overall (RR=1.31; p <0.001), in competition (RR=1.31; p <0.001) and in practice (1.29; p <0.001).(Smith, Myer et al. 2013) In a high school football population specific to the current pivotal study proposal, we also found a significant reduction in practice related, competition and total reported concussions (**Table 2**).(Smith, Myer et al. 2013) In a follow-up investigation, in professional football players, there was a statistically significant and clinically lower incidence of concussions for games played at altitudes above 644 feet.(Myer, Smith et al. 2014) Relative to game field elevation, there was a 30% reduced odds of concussion when playing at higher elevation compared to playing a game at lower elevation. The results of this study in professional athletes are consistent with the results of the previous study on high school football players.(Smith, Myer et al. 2013, Myer, Smith et al. 2014) To summarize the effect of all existing data, a recent and more encompassing meta-analysis was performed and published (**Figure 4**).

Safety testing in athletes has been approved by the local IRB and was completed in the

	Low Altitude			High Altitude		
	Practice	Competition	Total	Practice	Competition	Total
# of concussions	585	876	1,461	511	795	1,306
# of athletic exposures (AE)	1641185	330311	1,971,496	1,867,735	380,625	2,248,360
Rate per 10,000 AE	3.56	26.52	7.41	2.74	20.89	5.81
RR	1.3	1.27	1.28	referent category	referent category	referent category
95% CI	1.16, 1.47	1.15, 1.40	1.18, 1.37			
p-value	<0.001	<0.001	<0.001			

TABLE 2: Association between topographical elevation and concussions in high school football: Dichotomous topographical elevation categories are (low altitude) 0-644 ft, and (high altitude) >645 ft. *The National High School Sports-Related Injury Surveillance System, U.S., 2005/06-2011/12*

Cincinnati Children's Hospital Human Performance Laboratory *(IRB Study ID: 2013-2240; Clinicaltrials.gov: NCT02901028)*. Evaluation of monitored vital signs, biomechanics, cardiorespiratory capacity, postural control, dynamic stabilization, reactive index, concentration and cognition, memory, strength and power in a population of athletes showed no statistically significant adverse effect of wearing a mild jugular vein compressive neck collar compared to a sham arm band.(Myer, Edwards et al. 2013) Cumulatively, the pre and post safety measures indicate that neurologic parameters of executive function, eye-hand coordination, balance, memory, strength, power, oxygen uptake, cardio-metabolic measure and reaction times were unchanged following two hours of physical testing wearing the collar prototype.(Barber Foss, Clark et al. 2017, DiCesare, Barber Foss et al. 2017, Thomas, Edwards et al. 2017) Acceptance of the compression collar was not different in physiological biomarker response to the non-collared condition during maximal oxygen uptake and maximum effort power testing (Figure 5).(Myer, Edwards et al. 2013)

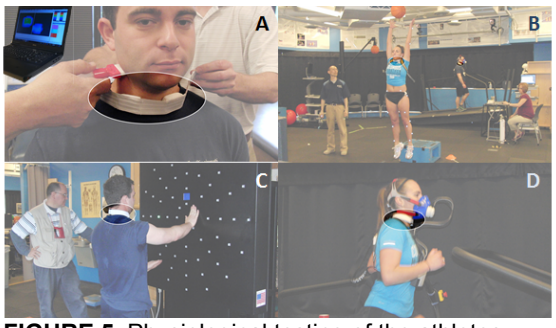


FIGURE 5. Physiological testing of the athletes while wearing the internal jugular vein compression device. Panel A shows the collar being fitted and evaluated for jugular pressures. In B, the athlete demonstrates that the collar does not impede full extension of the arms overhead during maximal power testing. C. The collar in place during Dynavision and (D), the collar during maximum oxygen uptake test.

Subsequent to the safety testing, Cincinnati Children's Institutional Review Board and the FDA panel determined that clinical investigation with jugular vein compression collar is a nonsignificant risk (NSR) device because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812).(FDA 2016)

An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (IRB Study ID: 2016-6895; Clinicaltrials.gov: NCT03236389). Magnetic Resonance Elastography was established at CCHMC in collaboration with The Mayo Clinic to support these studies. Under jugular vein compression with the collar, all participants tolerated the procedure without any untoward effects. Jugular vein compression via a passive collar device is a promising avenue for mitigating diffuse traumatic brain injury in collision sports and other impact-prone activities. Inspired by similar mechanisms found in woodpeckers and bighorn sheep, in principle the reduction of venous return increases intracranial blood volume and consequently mitigates the forces involved in coup and countercoup injuries. Here, we employed magnetic resonance venography (MRV),

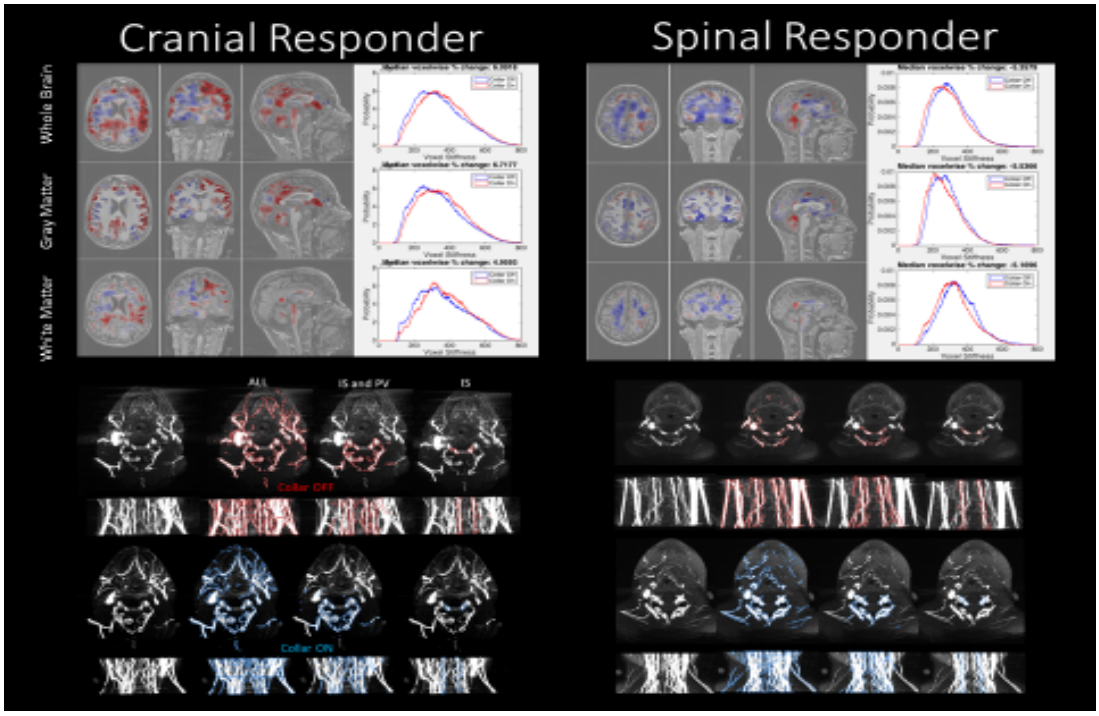


Figure 6. MRV images show successful restriction of jugular vein flow for cranial responder while also showing that recruitment of alternative pathways for venous return was achieved for spinal responder. Cranial responder showed increased stiffness as indicated by increased red response while limited increased stiffness (not likely to be reflected with cranial MRE) in the spinal responder who utilized alternative pathways for blood flow in response to jugular vein compression.

elastography (MRE), and imaging (MRI) to investigate whether the collar can modulate venous return, cranial compliance, brain tissue stiffness, and intracranial volume of cerebrospinal fluid (CSF). All images were acquired on a 3T GE Discovery system and processed in SPM12. Four participants (3 male, 1 female;19-24 years old) received the following neuroimaging battery:

two 3D T1-weighted scans (1 mm3 isotropic, TR/TE = 8.6/3.2 ms), two 2D MRE scans (1.875 x 1.875 mm in plane, 3.6 mm slice thickness, TR/TE = 2600/120.7 ms), and two 2D time-of-flight MRV scans (0.47 x 0.47 mm in plane, 6 mm slice thickness, TR/TE = 13.8/2.4 ms). Between repeated acquisitions, participants exited the scanner and put on/removed the collar, providing one image of each modality in a "collar-on" and "collar-off" condition. 2D scout images were acquired prior to each scan to achieve similar positioning and slice prescriptions for all acquisitions. Brain stiffness measures for collar-on and -off conditions were computed from the MRE images. On and off condition MRE magnitude images were co-registered for each subject using a normalized cross-correlation algorithm and the corresponding calculated stiffness images were multiplied by the resulting rigid body transformation matrices. Lastly, an 8mm Gaussian smoothing kernel was applied to approximate the effective resolution of the MRE scan at 25Hz. To calculate intracranial CSF volume for each subject and condition, the T2-weighed MRE magnitude image was co-registered using normalized mutual information and resampled to match the T1-weighted MRI scan. Both images were then used to generate tissue probability maps of gray matter, white matter, and CSF volume from SPM12's multi-channel unified segmentation algorithm. Analyses of these images provide preliminary evidence of the proposed protective mechanism of the collar. MRV images showed successful restriction of jugular vein flow for responder participants while also showing that recruitment of alternative pathways for venous return was achieved for non-responders (**Figure 6**). Notably, stiffness was not substantially changed for non-responder, but was increased for responder. Taken together, these multimodal imaging data provide initial, *in vivo,* evidence demonstrating a potential mechanism by which the collar changes the jugular vein blood flow and compliance and thus affects the vulnerability of the brain against acceleration/deceleration injuries. Furthermore, the differential responses of subjects may indicate a subject representing those who do not respond in the same way to the application of the collar in the physical properties of the jugular vein. Whether these subjects are representative of two potential distinct groups, cranial responder vs. spinal responders" to the collar usage, requires further investigation. For example, there is reasonable logic to presume that just the filling of the spinal vertebral venous space could be enough to impart the wanted protective action for the cranial space (and MRE would not be able to detect this spinal filling per say). However, the data presented in this report is a proof of concept for exploring the potential physiological mechanism by which the jugular vein compression helps to improve protection from brain injury in contact sports. If our results can be replicated and proved valid in future studies, the imaging variables could serve as valuable explanatory markers for real-world studies of collar use and ultimately be used as predictors of outcome.

An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (IRB Study ID: 2013-5717; Clinicaltrials.gov NCT02262507). We studied 410 participants (ages 12 to 68 years of age) via a middle ear power analysis (MEPA) with and without the compression collar, and no complaints or untoward effects were noted and no declines in the auditory perception were recorded. The expected changes of reduced Acoustic Reflectance of the inner ear and middle ear (indicative of reduced compliance) were noted only in a subgroup analysis of those with jugular vein compression. The results of this study indicate that the neck compression collar prototype may have the potential to safely reduce energy impartation into cranial structures (i.e., the inner ear); however, further work is needed with advanced collar designs to establish this effect.

fMRI and CO_2 reactivity was performed on 12 adults before and after application of jugular vein compression. Results comparing before and after jugular vein compressions (with the collar) yielded that compression of the internal jugular veins in supine healthy volunteers increases blood volume in the skull with venous blood distributed particularly to the large venous sinuses. Specifically, compression of IJV increases the blood volume in venous sinuses, observable in particular in the straight and sigmoid sinuses. This confirms the effectiveness of the IJV compression. Compression of IJV results in a small, but widespread reduction in BOLD signal over the brain. This observation is consistent with either a decrease in cerebral blood flow or increase in volume of deoxygenated blood. A small increase in the BOLD signal seen in the middle cerebral artery (MCA) and cerebellum indicated the possibility of a slightly increased cerebral blood flow or the accumulation of arterial blood diffusely as well. Jugular venous compression (JVC) does not change the magnitude or distribution of the resting blood flow in the brain and does not affect the response of brain blood flow to hypercapnia. This finding implies that it would not affect the brain blood flow in response to an increase in demand for flow. Further JVC does not reduce the cerebral blood flow CBF if applied during increase in flow demand, as simulated in this study by hypercapnia. This finding provides confidence that the brain would be able to maintain CBF if the collar is applied under other high flow states such as exercise (**Figure 7**).(Fisher, Duffin et al. 2013)

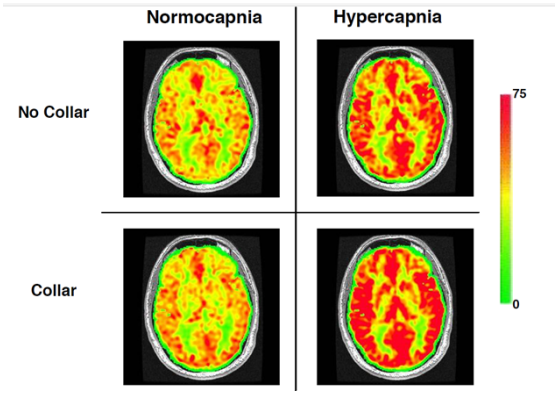


Figure 7: Mid-brain single slice ASL images for a single subject at both normocapnia and hypercapnia, with and without the collar. Color scale range from 0 to 75 in units of mL/100g/min.

An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (Study ID: 2014-5009; Clinicaltrials.gov: NCT02271451). The *in vivo* clinical trial was performed in hockey players of the proposed intervention device used during sporting competitions to test its effect in ameliorating neuroanatomical and neurophysiological changes to the brain using two widely accepted techniques [(DTI), and event related potentials (ERPs) utilizing electroencephalography.](Reches, Laufer et al. 2014) For athletes in the non-intervention group, RD (Song, Sun et al. 2003, Song, Yoshino et al. 2005) increased significantly from pre-season to mid-season. By comparison, the athletes in the intervention group did not show a significant change in RD with similar accumulated g-force head impacts **(Figure 8)**. In kind, ERP analysis showed concomitant changes in brain network dynamics in the non-intervention group—the level of change was strongly correlated with

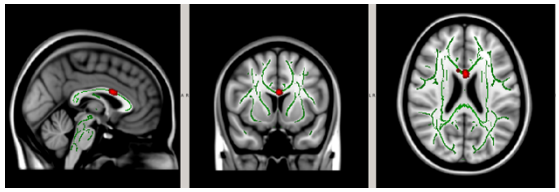


Figure 8 Significant alterations in MD (a) and RD (B) from pre- to mid-season in non-collar group after accounting for longitudinal changes in collar group. The red regions represent areas where the increase of DTI measure in the non-collar group was significantly larger than that in the collar group, $p < 0.05$ level (FWE corrected). The red regions are thickened to improve visual display.

the accumulated g-force of the collisions, whereas the intervention group showed no significant change. These group differences indicate that mild jugular vein compression may provide protection from the detrimental effects of collisions and resultant brain injury. These prospective longitudinal data utilized an internal (*in vivo*) approach and demonstrate, for the first time, that it is possible to protect the brain from sports related head impacts. (Myer, Yuan et al. 2016)

An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (Study ID: 2015-2205; Clinicaltrials.gov: NCT02696200) The *in vivo* clinical trial was performed in football players implementing the proposed intervention device used during sporting competitions to test its effect in ameliorating neuroanatomical changes to the brain evidenced by DTI. Based on pre-clinical data we hypothesized that collar, which imparted jugular compression that minimally restricts venous outflow to encourage cerebral venous sinus engorgement, would reduce brain injury biomarkers in athletes exposed to head impacts during a competitive football season. This project utilized a prospective controlled trial to evaluate effects of mild jugular vein (i.e., neck) compression (collar; n=31) relative to controls (no-collar; n=30) during a competitive football season (males; 17.04 ± 0.67 years). Helmet sensors were used to collect daily impact data in excess of 20 g (games and practices) and the primary outcome measures, which included changes in white matter microstructure, were assessed by diffusion tensor imaging (DTI). Specifically, four DTI measures including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were analyzed using a Tract-Based Spatial Statistics (TBSS) approach—a voxel based analysis. The final analyses included both an intent to treat (ITT) and per protocol evaluation of the collar intervention. The ITT analysis indicated a consistent vascular response by the athletes to collar compression, as indicated by internal jugular vein dilation (IJV) superior to its application ($p < .01$). Both groups experienced similar overall g-forces and total head impacts during the competitive football season (impacts > 20 g; collar 16983 vs no-collar 17750 ($p > .05$). Significant pre- to post-season reduction in MD, AD, and RD (corrected $p < .05$) was evidenced by extensive WM areas in the no-collar group, while no statistically significant longitudinal change was indicated for any of the DTI measures in any WM region in the collar group. Comparing the two groups, the no-collar group demonstrated significantly larger pre- to post-season DTI change in many WM regions (corrected $p < .05$) **(Figure 9)**. Correlation analysis also showed initial evidence of significant correlation between the change in AD in

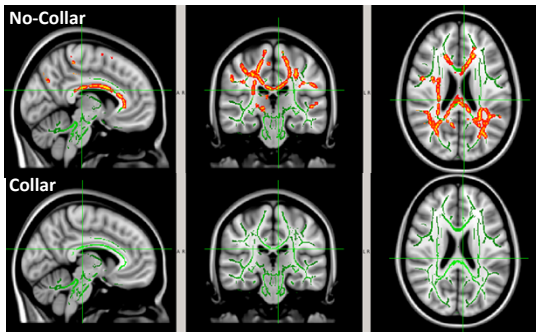


Figure 9. White matter regions with significant within-group AD reduction at postseason compared with preseason baseline. The significant regions (red-yellow regions, $p<0.05$, FWE corrected for multiple comparisons) were overlaid on to the white matter skeleton (green) and standard T1-weighted image in MNI 152 space (grey scale). The significant regions were filled in using tbss_fill in FSL to improve visualisation. Image orientation is in radiological convention. AD, axial diffusivity; CTRL, control; FSL, FMRIB Software Library; FWE, family-wise error rate; MNI, Montreal Neurological Institute. Top row: no-collar (CTRL) group; bottom row: collar group.

some WM regions and the number of impacts and/or the cumulative G-force experienced in the no-collar group (all $p<.05$). Per protocol, results were consistent with presented ITT findings with an expected increase in effect sizes noted in most voxel analyses. Our findings, based on four DTI measures known to relate to brain injury, indicate a consistent reduction of change in diffusivity parameters noted in the no-collar group at post-season. This reduction is consistent with and repeated in our studies and likely indicative of sub-clinical white matter injury due to repetitive head impacts during the competitive season. The smaller and statistically non-significant change in diffusivity in the collar group evidences a mitigating effect from the induced jugular outflow impedance. Restated, the approach to impede IVJ blood flow appears to have ameliorated the detrimental effects that resulted from a season of head impacts. The current study presents the first football related prospective longitudinal data and demonstrates a novel, in vivo, approach to protect the brain from football related head impacts. These results build on prior research and evidence the need for future work to determine if this novel method for brain injury prevention is both safe and effective.(Myer, Yuan et al. 2016)

An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (Study ID: 2015-2205; Clinicaltrials.gov: NCT02696200) The *in vivo* clinical trial was performed in football players implementing the proposed intervention device used during sporting competitions to evaluate effect of repetitive head impacts on the alteration of neuronal activity based on 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 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 ($p<0.05$) **(Figure 10)**. 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.(Yuan, Dudley et al. 2017)

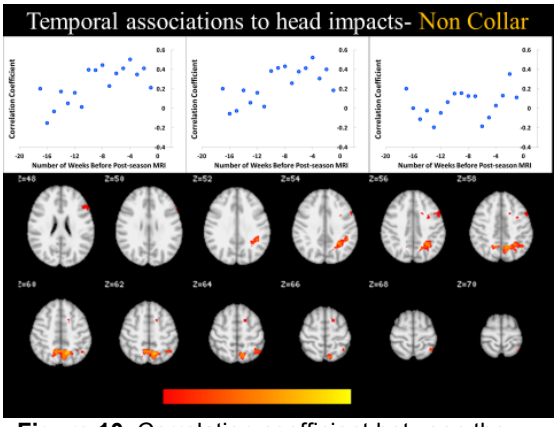


Figure 10. Correlation coefficient between the pre- to post-season change of brain activation and the weekly impact (A: number of hits; B: total g-force; C: Average g-force) experienced at different time prior to the post-season imaging. The X-axis denotes the week number before the post-season imaging, e.g., -1 represents the last week, and -4 represents the 4th week prior to the post-season imaging.

An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (Study ID: 2015-2205; Clinicaltrials.gov: NCT02696200) The *in vivo* longitudinal clinical trial was performed in football players implementing the proposed intervention device used during two sporting competitions to quantify the longitudinal persistence of altered white matter (WM) integrity observed in one high school football season at 8 months post season and to evaluate the long term effects of the jugular vein compression collar designed to ameliorate alterations in brain network. Prospective diffusion tensor imaging data from 23 male high school football athletes (10 non-collar; 13 collar) were acquired at three longitudinal time points: T1 (pre-season), T2 (post-season) and T3 (following the off-season). The in-season time interval (T1→T2) was 4.24±0.52 months and the off-season interval (T2→T3) was 8.48±0.30 months. Tract Based Spatial Statistics approach was used to quantify change in the WM anisotropic diffusion properties between these time points. DTI remained unchanged across all time points in the collar group. Despite similar number/severity of head impact, the non-collar group showed significantly greater reduction than the collar group in mean, axial and radial diffusivity between T1→T2 in extensive WM regions (corrected $p<0.05$). During the presumed recovery off-season period without head impact exposure (T2→T3), DTI diffusivity values in the non-collar group increased significantly toward baseline, but remained significantly lower (T1>T3; all $p<0.05$). The non-collar group demonstrated WM recovery towards baseline during the off-season relative to post-season DTI alterations found following the competitive football season. However, the persistence of significantly lower diffusion properties (again, in the non-collar group) may be indicative of incomplete WM recovery. The lack of significant DTI change over time in the collar group suggests that a mitigating effect may be afforded from the applied jugular compression.(Yuan, Barber Foss et al. 2017)

An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (Study ID: 2015-2205; Clinicaltrials.gov: NCT02696200) To evaluate the collar experience across a high school football season, a survey was created and distributed among the football participants. The survey was composed of three categories of questions: collar effect on performance, collar use and experience, and collar care and storage. Results were received from 31 of the participating high school football players to investigate their experiences when using the Q-Collar during the football season. Football players reported an overall positive experience using the collar, feeling an increased sense of protection when wearing the device (0% negative responses), perceived improved performance and heightened maximum effort on the field (0% negative responses), and most athletes reported that they would continue to wear the device if made available in the future (6% negative responses). Players also reported little to no discomfort or pain while wearing the device. While this study did not investigate the efficacy of the device in reducing mild TBI risk or changes in DTI surrogate endpoints among high school football players, it showed that this device is both usable and tolerable among a small, selective sample of high school athletes.(Roth, Cohen et al. 2017)

An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (Study ID: 2015-2205; Clinicaltrials.gov: NCT03014492). It is speculated that females may be at a particularly higher risk, prompting a prospective longitudinal controlled cohort study with a

novel jugular compression collar to determine its effects on long-term WM changes over three time-points spanning 9 months. DTI analyses revealed significant WM changes from pre- to post-season in the non-collar group in MD, AD, and RD but no significant change was found in the collar group, despite similar quantity and magnitude of head impacts. Significant correlation was found between head impact exposure experienced during the season and pre- to post-season DTI changes in the non-collar group. In addition, the WM changes in the non-collar group identified at the post-season time point partially resolved at 3 months offseason follow-up but remained significantly different when compared to pre-season. In conclusion, microstructural changes in WM as assessed by DTI were found to occur during a single season of high school female soccer athletes. These changes occurred in athletes in who did not wear the jugular compression collar but did not occur in those who wore the collar **(Figure 11)**. The mitigated WM alterations in athletes in the collar group suggested a potential effect of the collar in ameliorating the changes against repetitive head impacts. In addition, the in-season WM alterations were reduced within 3 months post-season indicating a physiological reversal in diffusivity changes noted during the competitive season in non-collar wearing participants.(Myer, Barber Foss et al. 2017)

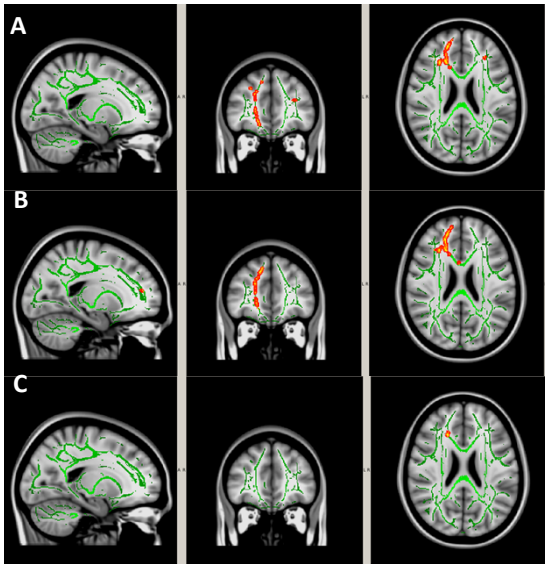


Figure 11. WM regions with significant group difference in the pre- to post-season reduction in (A). MD; (B) AD; and (C) RD between the 22 participants in the non-collar group and the 24 participants in the collar group who underwent both pre- and post-season MRI. The significant regions (red-yellow regions, $p<0.05$, TFCE corrected for multiple comparisons) were overlaid on to the WM skeleton (green) and standard T1-weighted image in MNI 152 space (grey scale). The significant regions were filled in using tbss_fill in FSL to improve visualization.

An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (Study ID: 2015-2205; Clinicaltrials.gov: NCT03014492). Recent neuroimaging studies have suggested that repetitive sub-concussive 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 is limited. In the current investigation, we aimed to (1) assess the longitudinal pre- to post-season changes in 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 non-collar group 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, an fMRI verbal N-Back task was

used to engage working memory. A significant pre- to post-season increase in fMRI 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 of head impacts during the season between the two groups (this signifies more work, O_2 uptake, was needed in the non-collared group to perform the same function). 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 **(Figure 12)**. 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.(Yuan, Leach et al. 2017)

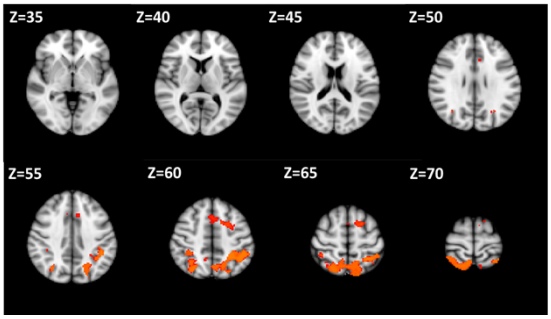


Figure 12. Brain regions with greater pre- to post-season increase in activation in non-collar group (n=21) than collar group (n=27, $p<0.05$, corrected) The z value in the upper left corner in all the panels represents the z-coordinate in mm.

An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (Study ID: 2016-8580; Clinicaltrials.gov: NCT03017937). This clinical study is aimed at determining the required minimum pressure at various locations on the neck to cause restriction of outflow of blood via the Internal Jugular Veins (IJV) in various targeted populations. The populations targeted in this study included males and females 7-60 years of age. Three test devices, each corresponding to a range of collar sizes, allowed for a controlled application of pressure to both sides of the neck. The fixtures were designed to universally fit participants 7-60 years of age and allowed local adjustments vertically along the neck. Two different pad sizes were evaluated with the size of pad being determined based on neck girth and corresponding Collar sizes, which were pre-defined. Study participants sat upright, and the IJV was identified via ultrasound. A sonographer performed vascular ultrasonography procedures of the neck for baseline measurements and sonographic images of the IJV on both sides with IJV compression. To address the first aim, the test fixture was applied to the participant's neck, with no pressure applied. The pressure was increased in increments of 0.1 +/- 0.025 lb. until the test fixture reads ~0.5 lb. IJV dimensions were captured and labeled based on the minimum pressure measured and the location of the test fixture. The second aim was addressed by applying new Q-collars of known force to the test participant, and confirming dilation of the IJV superior to the point of pressure, using ultrasound. This process included applying collars corresponding to the measured size, one size above and one size below the fitted collar. Data was captured on hard copy case report forms (CRFs), in an electronic database, and as sonographic images. IJV dilation compared to baseline was visually confirmed by registered vascular technologist, and the force applied by the test collar at the lowest responsive level was recorded. Following this subjective measurement, length, width and area of the responsive IJV was measured, using the ultrasound software, and a % difference was measured compared to baseline. IJV response to the Q-collar was also collected, measured, and compared to baseline. Visually confirmed forces corresponding to IJV dilation indicated a response of the IJV to the test collar and Q-collars. These responses were confirmed by measurements. The results indicated a positive response in >90 of study participants at 0.2 lb of IVJ pressure and that optimal response as evidence by IJV distention was noted in fitted collar **(Figure 13)**. The results of the current project indicate a universal response to IJV distention and the benefits of proper collar fitting to optimize IJV response.

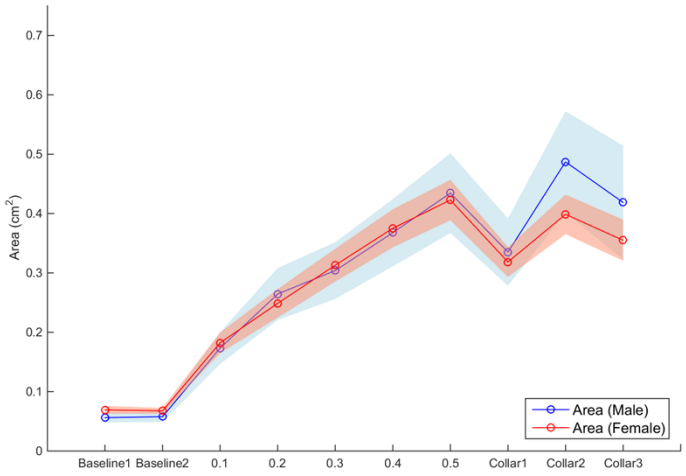


Figure 13. Internal jugular vein response to differential pressure applications of the tested collars.

Evidence from a previous pilot study indicates that repetitive head impacts from sports leads to changes beyond chance in three pre-defined DTI metrics (AD, MD, and RD) in student athletes.

This study aims are to:

- •Determine whether a neck collar that applies mild jugular vein compression designed to reduce brain energy absorption in head impact by evaluating three pre-defined DTI derived metrics following a full season.
- •Control for and correlate with head impact exposure with the three pre-defined DTI metrics.
- •Confirm collar user placement and compliance.
- •Confirm collar user safety.

(4) STUDY DESIGN:

The current project will be a prospective longitudinal study design as well as to include retrospective data from a previous study (IRB #2018-2799, entitled Evaluation of Helmet Technology and Head Impact Exposure). The subjects in 2018-2799 underwent the same testing as subjects in the current study and thus incorporating the data from the previous study will strengthen the results from the current study. All MRI scanning will be performed on a 3 Tesla Philips Achieva MRI scanner located in Imaging Research Center (IRC) in the Cincinnati Children's Hospital Research Foundation (CCHRF). Sedation will not be used for any of the test visits. The entire MRI series, which may include anatomical imaging, DTI, resting-state fMRI, and magnetic resonance spectroscopy (MRS) will take less than 45 minutes (see Table 3 for detailed specifications).

Table 3. Image sequence, mode and analysis. Imaging will be completed in 30 minutes or less.

Sequence	Resolution	Mode	Analysis	Time (min)
3D T1	1x1x1 mm	Anatomy	Visual /Volumetrics/registration	5
DTI	2x2x2 mm	WM microstructure	Visual/ROI/TBSS/structural connectivity	12
fMRI	2.5x2.5mm	Blood Flow	Functional Connectivity	5
MRS	Single Voxel	Neural Integrity	Neurometabolic function of M1	5
MRS	Single Voxel	Neural Integrity	Neurometabolic function of DLPFC	5
MRS	Single Voxel	Neural Integrity	Neurometabolic function of ACC	5
			Total Time	~37 min

(5) DURATION:

The study recruitment and intervention will occur during one season. Each participant will participate in 2 planned study visits that may take up to 1 hour. Data analysis will continue for a 2 year period following the final enrollment.

(6) SELECTION & RECRUITMENT OF PARTICIPANTS:

We will recruit up to 500 study participants (250 per sport). The participants (age 13-19 years old) will be recruited from local school districts. Participants will be recruited using a top-down approach. We have gained the consent and the cooperation of the school district administrations. Presentations and letters from the research team will be given to each participating school to detail the participation requirements and study risks. Questions regarding participation will be answered during the presentations or through e-mail or phone. Participants will be contacted via telephone or email to further explain the study, answer any additional questions and to enroll them in the study. Participants also have the option of completing an electronic eligibility screener. Qualifying participants may then choose to provide their contact information for research staff to contact them about potential participation. The demographic forms will be distributed to parents to complete at the coaches/parent meeting or when the subject is enrolled. The participants and parents/guardians who voluntarily agree to participate will be scheduled to complete the pre-participation testing. The participant and parent/guardian will read and sign the "Consent to Participate in a Research Study" form, approved by the Institutional Review Board of Cincinnati Children's Hospital. If the participant and parent/guardian does not read or sign the form, they will not participate in the study. Once the potential school teams are identified, they will be randomized to one of two groups: 1) Device wearing during the season or 2) Non-device wearing during the season. This research does not mandate that the participant maintains participation in their sport. The desire to participate in the sporting event is an independent, personal decision separate from the decision to enter into this study. If any athlete choses to stop participation in the sporting activity then they will also be withdrawn from the study, due to no longer meeting inclusion criteria. We will also enroll a group of athletes involved in a non-contact sport (such as cross-country) as no head impact controls (N=40).

Inclusionary criteria include:

- Normal healthy volunteer
- Able to provide written consent
- Must be 13 years or older and a participant on a high school football or soccer team

Exclusionary criteria include:

- Unable to provide written consent
- History of neurological deficits, previous cerebral infarction, or severe head trauma as indicated through pre-season screening:
- Medical contraindications to restriction of venous outflow via the internal jugular veins (known increased intracerebral pressure, metabolic acidosis or alkalosis)
- Glaucoma (Narrow Angle or Normal Tension)
- Hydrocephalus
- Recent penetrating brain trauma (within 6 months)
- Known carotid hypersensitivity
- Known increased intracranial pressure
- Central vein thrombosis
- Any known airway obstruction
- Any known seizure disorder
- Prothrombotic or hyperthrombotic condition
- Cerebral cavernous malformation
- Players not medically cleared to play sports

Waiver of Documentation For all potential participants that are invited and/or screened by phone, mail, e-mail or eScreener, we are requesting a waiver of documentation of consent for the Screening Phase of the study. Screening and questionnaire completion are minimal risk activities and typically done in the clinical setting without consent. Completion of the eligibility screen and questionnaires prior to the participant's arrival will decrease the overall time spent in the study visit.

(7) PROCESS OF OBTAINING CONSENT

Once a participant is identified as a potential participant, is contacted by a CCHMC/Sports Medicine representative and verbally agrees to participate, the process to obtain consent will begin. A copy of the informed consent will be provided to the participant at this time. The study coordinator will review the informed consent and the participant will have an opportunity to ask any questions regarding the study and/or the study protocol. At that time, the participant will be given time to decide whether or not they wish to participate and if so, asked to sign the informed consent. Once the signature is obtained, the participant will be given a copy of the consent and testing will commence. At no time will the participant be coerced into participation. Receiving the informed consent prior to enrollment will allow the participants to review the study information prior to participation in the study. This will aid the participant to make an informed, unforced decision regarding election to participate in the study.

Because we will be testing teens, we will be using the Parent Consent Form to obtain both the participant assent and the parent consent. The participants and their parents will be given adequate time to review the study materials and ask questions. If they choose to participate, the patient and parent will sign the IRB approved consent forms. It will be made clear to the patient and their parents that participation in the study is voluntary. Subjects aged 18 and over will complete the Adult Subject consent form.

In the event that a parent or guardian will not be present at the scheduled testing appointment, consent/assent forms will be provided ahead of time for review for those subjects under age 18. The coordinator will ensure that all necessary forms have been signed prior to any data collection.

Parents of study participants may complete a brief behavioral rating scale that assesses symptoms of ADHD (See Procedures section). We will send parents a link via email for them to complete this questionnaire via a REDCap online survey. This questionnaire will take no longer than 5-10 minutes for the parent to complete. The Concussion in Sport Group panel has recognized numerous mTBI "modifiers" (e.g., sex, age, ADHD) that can impact the severity of the mTBI and course of recovery. The presence of ADHD has been associated with greater likelihood of mTBI occurance, as well as experiencing multiple mTBIs. An ADHD diagnosis is also associated with worse symptom severity and prolonged course of mTBI symptom recovery, compared to non-ADHD cohorts. However the effects of ADHD on repetitive head impacts and sub-clinical threshold head impact exposure is unknown. The current study will help uncover the potential effect of co-morbid ADHD on the study outcomes.

(8) STUDY PROCEDURES:

Study Visit and Brain Imaging-Performed at CCHMC Imagining Research Center may contain the following tasks:

MR imaging data Acquisition

Magnetic Resonance Imaging (MRI), including sequences outlined in Table 3 are all based on the concept of using magnetic fields and radio waves to make chemical, anatomical and physiological assessments with in the living tissue. This technology has been utilized for diagnostic and research purposes since the early 1980s.

This testing will consist of a minimum of 2 MRI sessions (preseason, and post season) all inside a 3T scanner at the CCHMC Imaging Research Center. During the acquisition of MR images, the study participants will lie on the scanner table. For most portions of MR acquisition, the study participants will only be instructed to lie still. For other parts of the acquisition, study participants will be asked to answer questions that will assess their cognitive ability and working memory. Participants will be allowed to communicate with the MR operator via an always-on, two-way intercom at any time. In addition, the participants have a hand-held air ball to squeeze in the event that they elect to be removed from the magnet immediately. The study participants have control over their presence in the magnet, which in turn tends to minimize feelings of claustrophobia. As magnetic resonance imaging employs the use of strong magnets, patients will receive a standard preoperative screening questionnaire

regarding the potential for ferromagnetic objects within their bodies to ensure their safety during the study.

Participants will be screened for MRI specific contraindications such as:

- Braces or permanent metal dental work
- Insulin pump
- Cardiac pacemaker
- Cochlear implants
- Hearing aids
- Aneurysm clips
- Orthopedic pins, wires, screws, or plates
- Any other exclusionary criteria as documented on the MRI safety screening poster included with recruitment materials

Those participants with any aforementioned contraindication will be excluded from the imaging portion of the study but will still be eligible to participate in the rest of the study procedures.

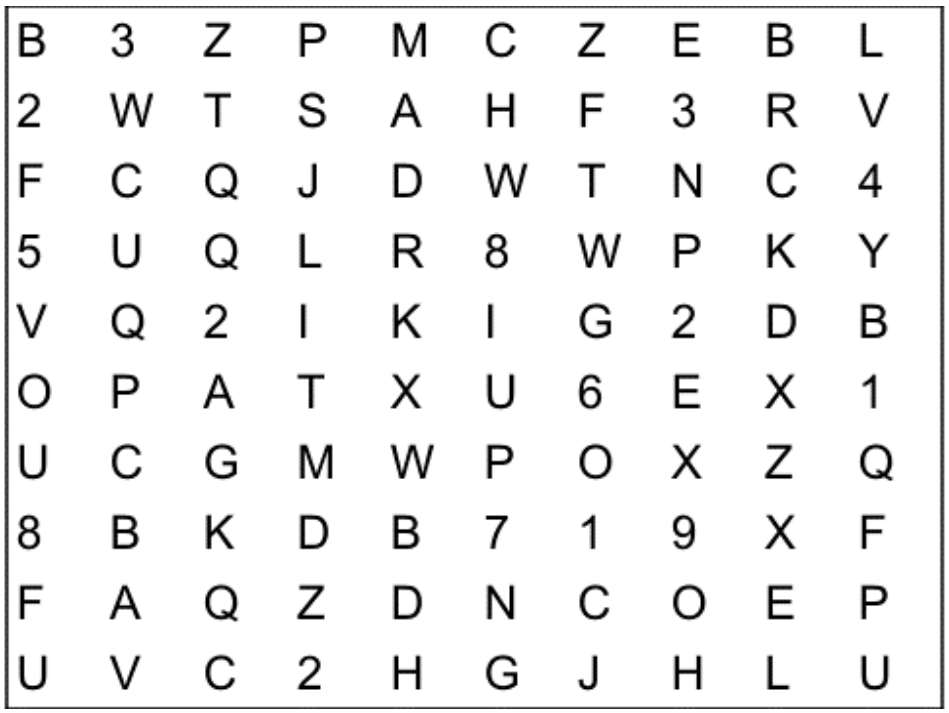
Functional Assessments of Neurovisual endpoints.

The MRI data will provide anatomic and inferred functional information concerning putative brain changes pre to post season. Additional and complimentary functional information will be obtained using following neurofunctional tests. These are outlined below.

1. Visual Evoked Potential (VEP).
2. Timed Saccades.

VEP: VEP is a method to assess the relative time and voltage involved in a flash to each eye individually and the response received at the occipital lobe. It is based on electroencephalogram (EEG) technology. The VEP accumulates 100 flashes and averages the responses obtained. The primary outcome measures are the N75 and P100 latencies and the signal amplitude as measured by the Reteval system (Roland systems Chicago IL). The system uses a hand held device that flashes light in one eye at a time and measures the responses. It is capable of doing multiple colors of light, in this case it will flash white light. A total of three EEG type Electrodes are placed relative to bony landmarks (mid forehead, lambda suture and inion. For electrode placement, the surface of the scalp is cleaned using NuPrep abrasive skin prep gel at the location of each electrode. Surface electrodes are fixed to the scalp using Conductive Neurodiagnostic Electrode Paste and standard surgical tape. Signal averaging is automatically processed by the system and stored on the hand held device and downloaded to a computer for further analysis. No mydriatic solution is used. The test is performed monocularly by placing an opaque patch over the unstimulated eye. The covered eye is kept open and hidden from light throughout the test.

Saccades: Saccadic eye movement is a critical component for activity of daily living, especially for school aged individuals who are reading and studying. We will use the 10 x 10 saccadic eye charts.



B	3	Z	P	M	C	Z	E	B	L
2	W	T	S	A	H	F	3	R	V
F	C	Q	J	D	W	T	N	C	4
5	U	Q	L	R	8	W	P	K	Y
V	Q	2	I	K	I	G	2	D	B
O	P	A	T	X	U	6	E	X	1
U	C	G	M	W	P	O	X	Z	Q
8	B	K	D	B	7	1	9	X	F
F	A	Q	Z	D	N	C	O	E	P
U	V	C	2	H	G	J	H	L	U

The subject reads alternating columns going down. So for the figure above the person would read: B, L, 2, V, F, 4 etc. The conclusion of the test is when the subject reads H, G. The test is timed and the time recorded. The result from the test is a time in seconds.

King Devick Test: The K-D test involves reading aloud a series of single digit numbers from left to right on three test cards. Standardized instructions will be used and the test requires less than 2 min to administer. Specifically, participants will perform a timed, two-minute test wherein participants are asked to read aloud single digit numbers separated by lines and arrows printed on test cards. This test will be performed twice. The test cards become more challenging as the spacing between numbers becomes more variable. The K–D test will include one demonstration card and three test cards. Participants will be asked to read the numbers on each card from left to right as quickly as possible but without making any errors. The sum of the three test card time scores will be used to create a summary score for the entire test. In addition the numbers of errors made in reading the test cards are also recorded.3 The fastest time will be recorded.

Near Point Convergence: We will assess near point of convergence (NPC) on all participants in order to compare these measurements with the oculomotor measurements. The NPC is a measurement that pertains specifically to visual fusion. Fusion is a visual term that refers to binocular vision. More specifically, fusion pertains to combining the image from the left and right eye synchronously to produce a single image. NPC is the closest point in space for which an individual can hold visual fusion. NPC is measured by bringing an object close to the nasal bridge. Once that image becomes blurry or double vision ensues, this is marked as the NPC break (measured in centimeters from the nasal bridge). NPC recovery can also be measured as the distance from the nasal bride when binocular vision ensues. Normal NPC break in youth is reported to be 5-6 cm with NPC recovery being 7-9 cm. NPC will be measured using a Gulden

Near Point Rule (http://www.guldenophthalmics.com/products/index.php/near-point-rule.html). The rule is placed on the patient's forehead with accommodation card at eye level. The accommodation card is brought towards the patient's nasal bridge. When the patient reports that he or she can no longer maintain binocular single vision (object becomes blurry), this is marked as the NPC break (distance from nasal bridge to accommodation card measured in centimeters). The NPC recovery is measured when the accommodation card is brought away from the nasal bridge. When binocular single vision is resumed, this is marked as the NPC recovery (distance from nasal bridge to accommodation card measured in centimeters).

Cognitive Testing*:*
Cued task switching. Participants are instructed to match a stimulus presented in the upper center of the screen to one of two stimuli in the lower left and right corners of the screen. In *task-homogeneous* (i.e., single task) blocks, participants match the upper stimulus to shape only (Task A) or color only (Task B). There will be 6 blocks. Participants switch between the two tasks (A, B) pseudo-randomly during task-heterogeneous (i.e., mixed) blocks. Each block contains 12 trials. Each trial will last for approximately 3700-ms. Presentation of task block type will be CACCBC. Participants will be instructed which type of task to complete prior to each block. The cued task switching task will take approximately 7 minutes to complete.

Digital Trail Making Test (dTMT). The digital version of the Trail Making Test is nearly identical and uses the same instructions to the standard paper version with the exception of replacing 'pencil' for 'stylus' and 'page' for 'screen.' Both parts of the dTMT consist of circles distributed over a tablet screen laid flat on a table. In Part A, the circles are numbered 1 – 20, and the participant should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 10) and letters (A – H); as in Part A, the participant draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The participant is instructed to connect the circles as quickly as possible, without lifting the stylus from the tablet screen. The dTMT is an Android-based app that was created to automatically extract participant performance features (see Dahmen, Cook, Fellows, and Scmitter-Edgecomb, 2005) including number of errors, time to completion, number of pauses, average pause duration, number of lifts, average lift duration, time inside each circle, and time between circles. Timing begins as soon as the stylus makes contact with the tablet screen and stops as soon as the last circle is touched. If the wrong circle is entered a red X is presented over the circle and the administrator informs the participants that a circle was skipped and to return to the last circle. The dTMT (both parts) will take 5 minutes.

Flanker Task. The flanker task assesses the orienting, alerting, and executive/conflict attention networks. Each trial begins with a central fixation cross. The target array is a set of five arrows presented horizontally in the center of a computer screen. The participant is to respond based on whether the central arrow is pointing to the left or right by pressing the corresponding left or right key on the mouse. On congruent trials the flanking arrows are pointing in the same direction, on incongruent trials the flankers point in the opposite direction from the central arrow, and on neutral trials the central arrow appears alone. Each target is preceded by one of four warning cue conditions: a center cue, a double cue, a spatial

cue, or no cue. In the center cue condition, an asterisk is presented at the location of the fixation cross. In the double cue condition, an asterisk appears at the locations of the target above and below the fixation cross. Spatial cues involve a single asterisk presented in the position of the upcoming target. A session of the ANT consists of a total of 24 practice trials and one experimental blocks of 96 trials in each. Participants indicate their responses via a right or left keyboard button-press. Accuracy and reaction time are recorded. Each trial begins with a fixation period of a random variable duration of between 400 and 1600ms. Subsequently, on some trials a warning cue is presented for 150ms. A brief fixation period of 450ms appears after the disappearance of the cue, followed by either the simultaneous appearance of the target and flanker, or by the appearance of the target alone. This display remains on the screen until a response is detected, to a maximum of 1700ms. After responding, the participant receives auditory and visual feedback from the computer. This task will take 5 minutes to complete.

Postural Sway Task: Participants will be asked to stand upright on a force platform. The force platform is a noninvasive device that measures the ground reaction forces produced during upright stance. Specifically, participants will be asked to stand comfortably with their arms at their side for a minute for two trials. Once with their eyes open and once with their eyes closed. There are no potential risks beyond those experienced during everyday upright bipedal stance (e.g., fatigue, falling, etc.). There are no direct benefits for the participants; however, participants may indirectly benefits from the opportunity to investigate the relationships among motor control, concussions, and brain activation.

Questionnaires:

Strength and Weaknesses of ADHD-Symptoms and Normal-Behavior scale (SWAN): Parents and study participants may complete a brief behavioral rating scale that assesses symptoms of ADHD via a REDCap online survey to be completed prior to the MRI scanning session. Parents that do not attend the MRI session with the research participant will be sent a link via email for them to complete this questionnaire. This questionnaire will take no longer than 5-10 minutes to complete. This will be completed at both the pre and post-season appointments and post-concussion. The SWAN consists of 18 items to measure ADHD symptoms. The 18 DSM-5 ADHD symptoms in the SWAN rating scale have been adapted to measure attention, as opposed to inattention, and positive impulse control, instead of lack of impulse control. Participants rate items on a seven point scale (1 = “far below average,” 2 = “below average,” 3 = “slightly below average,” 4 = “average,” 5 = “slightly above average,” 6 = “above average,” 7 = “far above average”).

PCSI: Parents and study participants will complete the Post Concussion Symptom Inventory (PCSI) form at the MRI screening session at both pre and post-season. The PCSI is used to assess for mTBI symptom severity at baseline and post-testing and post-concussion. The PCSI is comprised 20 questions assessing common symptoms of mTBI. Symptoms were rated on a seven point scale ranging from 0 (“not a problem”) to 6 (“severe problem”). Four factor scores are derived by summing items on each factor: Physical (8-items; e.g., “complains of headaches”), Fatigue (3-items; e.g., “sleeping more than usual”), Emotional (4-items; e.g., “acts irritable”), Cognitive (5-items; e.g., “has difficulty concentrating”) symptoms.

Exposure Questionnaire: Study participants may complete a brief REDCap survey to collect the participant's previous exposure to contact or collision sports. The Exposure Questionnaire is based on the subject's participation in school- or club-based sports in their lifetime. Participants were asked to select sports they have participated in any sport from a list sports with a high risk of concussion. For each sport the participant selected, they were asked at which ages they participated in the identified sport and for how many hours per week they participated in that identified sport. This online survey will be completed prior to the MRI scanning session. This questionnaire will take no longer than 5-10 minutes to complete. This will be completed at the pre-season appointment only.

TBI History Questionnaire: Parents and study participants will complete a brief REDCap survey to collect participant's history of TBI. The TBI History Questionnaire assesses the lifetime history of traumatic brain injury (TBI). The questionnaire elicits recall of head or neck injuries requiring medical attention, as a result of a motor vehicle accident, or from falling or getting hit by something or someone. For each identified head or neck injury incident, the participants are asked if they experienced (1) a loss of consciousness and for how long (i.e., <30 minutes, 30mintues to 24 hours, >24 hours), (2) feeling dazed or a gap in their memory from the injury and for how long, (3) nausea, vomiting, severe headaches, memory problems and/or dilated eyes and for how long, and (4) if they missed any school/work or other activities because of these symptoms. This will be completed at the pre-season appointment only.

If participants fail to complete any portion of the questionnaires during their study visit, we will contact them via email to obtain this missing information.

Injury Surveillance

Device and Compliance Acceptance: The study coordinator will be responsible for providing the appropriate intervention (device or no-device) to each team based on their random assignment prior to the season onset. At first fitting of the collar a registered vascular technologist will utilize ultrasound to ensure that the collar fits correctly and is activated as prescribed. Following the initial fitting, each athlete will receive adequate instruction on how to properly use the device on a daily basis. Throughout the season, the coordinator will make routine visits to each team to monitor the proper usage and fitting of the device, tracking the use of the device by each athlete individually. At the end of practice/game the device will be collected by the athletic trainer and/or stored in the athlete's locked locker. The device is not to go home with the athlete.

Head Impact Surveillance and Follow-up: All players will wear an accelerometer (CSx Systems, Auckland, New Zealand) to measure the magnitude of each head impact sustained by the subject. The accelerometers are equipped with electronics that allow for the measurement of linear accelerations and rotational velocities of the head. The accelerometer measures six degrees of freedom by directly measuring three axes relative to linear acceleration and three axes relative to angular velocity. The accelerometer stores all data locally for uploading to a computer. De-identified impact data are transmitted to a cloud-based server,

accessible only to the study research team via a unique username and password. All impacts greater than a preselected threshold between 15-20 g-force will be recorded and utilized in the postseason analyses. If available, video of games and practices will be used to validate and confirm head impacts recorded by accelerometers. Accelerometer tracking and management will occur at every game and practice by the study research team.

The study participants will also be monitored on a weekly basis for athletic exposures for a single season. The data secured regarding each athlete's participation in individual practices and games combined with accelerometer exposure to impacts allows the research team to capture robust individual athlete exposures rather than just combined team exposures.

The athletic trainer will evaluate any athlete for whom a concussive event has been observed (within 24 hours). Should the MD concur with the AT on a positive evaluation, a diagnosis of isolated concussion is made and the athlete is removed from play and participant is referred for to a post-concussion evaluation.
Post-concussion and post season testing consists of the same battery of tests as performed for pre-season testing, which allows for direct comparison between typical and concussed data.

Concussion follow-up: The data collection for this study was completed successfully as proposed in the original IRB. We collected neuroimaging data from over 400 participants at both pre-season and post-season. For those who experienced concussion, we also collected neuroimaging data soon after the concussion. During the 2018 football and soccer season, a total of 41 participants experienced concussion. From our preliminary data analysis, we have found significant pre-season to post-concussion changes in the brain network and we also found that the collar wearing at the time of concussion showed significant mitigating effect to these changes. The initial finding has been reported in a recent abstract submitted to a scientific meeting (see reference below). In the present amendment, we propose to conduct follow-up scans in these children with concussion experienced in the past sports season before the new sports season starts. Our goal is to quantify the degree of abnormality preserved in these athletes before the new season starts. The progression of the change observed in brain network, from post-concussion, to post-season, and then the follow-up at approximately 6-9 months after injury, will allow us to generate significant data critical for future prospective extramural grant applications focusing on the sports related concussion and recovery. We will use the same MRI protocol as in the original study. The MRI protocol will include the following sequences: 3D T1w, DTI, rs-fMRI, and MRS, which will be approximately 40 minutes in total in scan time. All the sequence specifications will remain unchanged. No sedation will be used during the scan. In addition to the MRI scan, we will also collect information regarding participation in contact sports between the end of last season and the proposed follow-up scans.

Myer GD, Barber Foss KD, Dudley JA, Diekfuss JA, DiCesare CA, Logan K, Leach JL, Yuan W. Brain white matter alteration in structural integrity and connectivity following a sports-related concussion: evaluation of the potential ameliorating effect of a jugular vein compression collar device. The 7th Annual Meeting for Pediatric Research in Sports Medicine Society, Glendale, Arizona, January 23-25, 2020. Submitted.

Following the competitive season/end of study participation, the collar study device will be returned to the study coordinator. No participant will be allowed to keep the study device once study participation has concluded.

(9) DATA ANALYSIS/METHODS:

Data Storage.
The personal demographic data for each participant will be blinded from the researchers, and a coded identification number will be used to track all collected data. Data will be stored on password-protected computers and only pertinent research personnel will have access. Data forms will be stored by coded identification number in a locked cabinet to which only pertinent research personnel have access. All data will be collected for research purposes only.

Statistical Analysis.
All analyses will be conducted according to a prospectively approved Statistical Analysis Plan. All analyses will be conducted in accordance with ICH E6 under pre-existing standard operating procedures. All analyses will be performed using SAS Version 9.1 or later. A two-sided p=0.05 is required to reach statistical significance.

All effectiveness data is expected to be continuous. Intra-group comparisons will be analyzed using a one-sample t-test while all inter-group comparisons will be analyzed using a two-sample t-test. Group differences will be tested using ANCOVA; baseline covariates include group, age, cumulative playing time, hit counts, hit intensity, and intensity per hit. Results will be presented for FA as well, but no FA effectiveness claims will be made.

All players will be included in all analyses to the fullest extent possible, consistent with the intent-to-treat principle. Repeated measures will be used to simultaneously evaluate the three pre-defined DTI metrics (AD, MD, RD).

Subgroup analyses will be performed for those playing >50% of all possible minutes for the position played as well as collar compliance, players dropping out due to injury or other reasons, and motion artifacts.

Data processing and analysis will be performed using a series of existing software including FSL (FMRIB's Diffusion Toolbox in FSL Software, Oxford, UK), AFNI (Cox, 1996) , SPM (Statistical Parametric Mapping analysis package, Wellcome Department of Cognitive Neurology, London, UK), DTIStudio (John Hopkins University, Baltimore, MD; Jiang et al., 2006), as well as additional customized software written in Matlab or IDL.

DTI data will first be subjected to preprocessing to correct for Eddy current and head motion artifact, followed by calculation of the three diffusion eigenvectors and eigenvalues. DTI measures, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) will be calculated. The regions of interest will be manually determined in major white matter areas such as corpus callosum, internal capsule, and external capsule. After being normalized to a common template, voxel based group analysis can be

performed to explore brain regions that present significant group difference or longitudinal changes. Fiber tracking can be performed to generate white matter tracts in different areas in the brain, e.g., cortico-spinal tract, different segments in corpus callosum, optic radiation, cingulum superior longitudinal fasciculus, and others.

Statistical considerations. The following calculations summarize the effect sizes which can be detected with the proposed sample size per intervention (collar users, non-collar users). The mean difference between collar users and non-collar users will be of primary interest. Effect sizes >1 are expected for each of AD, MD, and RD.

Soccer:

Group Specific: With 40-60 subjects per group subset (separately for collar users and not collar users), the following intra-group deteriorations (BL->EOS) can be detected with 90% power and two-sided 5% Type I error; small (<0.3) effect sizes for the change from baseline within a group (either non-user change or no collar user change) can be detected; a 15% loss can be accommodated to retain 80% power:

One group t-test: Mean change = 0

	90% Power		Reach Significance	
	1	2	3	4
Test significance level, α	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2
Effect size, $E = \lvert m_A - m_0 \rvert / SDW$	0.526	0.425	0.318	0.257
Power (%)	90	90	NA	NA
N	40	60	40	60

Group Comparisons: With 40-60 subjects per group, the following inter-group comparisons (at EOS) can be detected with 90% power and two-sided 5% Type I error; a moderate (0.3-0.5) effect size for the treatment difference will result in reaching statistical significance for testing the above pre-specified hypotheses (a pre-specified treatment group difference at a pre-specified time); a 15% loss can be accommodated to retain 80% power:

Two group t-test: Mean difference = 0 (equal n's)

	90% Power		Reach Significance	
	1	2	3	4
Test significance level, α	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2
Effect size, $E=\|m_1-m_2\|/SDB$	0.734	0.597	0.444	0.361
Power (%)	90	90	NA	NA
n per group	40	60	40	60

Type 1 Error Control: There will be multiple effectiveness endpoints which require Type I error control for multiple comparisons. Hierarchical strategies will be used. The overall Type 1 error is two-sided p=0.05. The primary hypotheses for the three pre-defined DTI metrics (excluding FA) will first be assessed. All three pre-defined DTI metrics must each achieve statistical significance in order to achieve study success. Based on historical data, there are many factors (compliance, mouth braces, MR head motion, not making sports team, sports related injury) that limit final per protocol follow-up assessments, therefore we will recruit up to 250 soccer athletes to ensure adequate sampling to support the study aims.

Football:

It is assumed that each school will have 48-72 participating players allowing a comparison of 48-72 players using the neck collar vs. 48-72 players not using the neck collar.

Group Specific: With 48-72 subjects per cohort-group subset (separately for collar users and not collar users), the following intra-group deteriorations (BL->EOS) can be detected with 90% power and two-sided 5% Type I error; small (<0.3) effect sizes for the change from baseline within a group (either non-user change or no collar user change) can be detected; 15% loss can be accommodated to maintain 80% power:

One group t-test: Mean change = 0

	90% Power		Reach Significance	
	1	2	3	4
Test significance level, α	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2
Effect size, $E=\|m_A-m_0\|/SDW$	0.478	0.387	0.289	0.234
Power (%)	90	90	NA	NA
N	48	72	48	72

With 48-72 subjects per group, the following inter-group comparisons (at EOS) can be detected with 90% power and two-sided 5% Type I error; a moderate (0.3-0.5) effect size for the treatment difference will result in reaching statistical significance for testing the above pre-specified hypotheses (a pre-specified treatment group difference at a pre-specified time); a 15% loss can be accommodated to retain 80% power:

Two group t-test: Mean difference = 0 (equal n's)

	90% Power		Reach Significance	
	1	2	3	4
Test significance level, α	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2
Effect size, $E=\|m_1-m_2\|/SDB$	0.669	0.544	0.404	0.329
Power (%)	90	90	NA	NA
n per group	48	72	48	72

Non-Head Impact Controls:
Based on the overall study, effect sizes indicated in the 2-sample t-tests, we will enroll and monitor 40 non head impact control participants (e.g. cross country) involved in training exercise to evaluate with the contact sport athletes The comparisons for the athlete group in non-contact sports will be used to account for the potential brain change resulting from exercise so that the change in the non-collar contact-sport athletes can be attributed to head impact experienced during the season.

Type 1 Error Control: There will be multiple effectiveness endpoints which require Type I error control for multiple comparisons. Hierarchical strategies will be used. The overall Type 1 error is two-sided p=0.05. The primary hypotheses for the three pre-defined DTI metrics (excluding FA) will first be assessed. All three pre-defined DTI metrics must achieve statistical significance in order to achieve study success. Based on historical data, there are many factors (compliance, mouth braces, MR head motion, not making sports team, sports related injury) that limit final per protocol follow-up assessments, therefore we will recruit up to 250 football athletes to ensure adequate sampling to support the study aims.

Statistical analysis of outcomes measures will be done using SAS®, version 9.3 (SAS Institute, Cary, NC) and SPSS statistical software (SPSS Inc, Chicago IL). Comparisons between the testing conditions (collar vs. no collar) will be made using Analysis of Covariance, in order to control for time (pre vs post season) and condition (collar versus no collar). We will also conduct correlation analysis to test the association between imaging biomarkers (as described above) with the results obtained from the impact surveillance. The collision indices, including total number of collisions, number of collisions from front, back, left, right, top, bottom, G force, and timing of each collision will all be recorded and tested in the analysis. Secondary analysis to compare the intervention with no intervention and calculate the rates would involve a Poisson model, using an offset to account for the playing time and exposure to concussive impact for each of the study participants. We will calculate the rate and the associated 95% confidence interval. SAS®, PROC GENMOD will be used for analysis, which allows us to account for the fixed and random effects, use the appropriate link function, and the offset for amount of playing time exposure.

For additional data analysis with a larger sample size, de-identified from Study 2018-2799 will be combined with this dataset. Data were collected with identical methods in order to support aggregate analysis of associated outcomes. Our rationale to include a larger sample

from 2018-2799 is to provide more robust results to the scientific community. Neuroimaging analyses require large sample sizes as 'trending or preliminary findings' often do not reach significance due to corrections for multiple comparisons (1000's of analyses require very conservative p values). More specifically, a larger sample size will provide us the opportunity to identify additional white matter regions with new features (location, volume, direction of DTI change) and their association with head impact exposure (linear and rotational acceleration).

(10) FACILITIES AND PERFORMANCE SITES:

All MRI scanning will be performed on a 3 Tesla Philips Achieva MRI scanner located in Imaging Research Center (IRC) in the Cincinnati Children's Hospital Research Foundation (CCHRF). Sedation will not be used for any of the test visits. The entire MRI series, including anatomical imaging, 3d T1, DTI, will be completed in 30 minutes or less (see Table 1. for detailed specifications).

(11) POTENTIAL BENEFITS:

Participants of this study will not receive any direct or immediate benefits by completing this study. However, they will be contributing to research involving the potential for major contributions to future TBI/concussion prevention strategies.

(12) POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS:

The Device partially circumnavigates and compresses the neck in the same way that a compression garment (non-medical apparel) behaves, and very similar to the compression exerted by a necktie (although this device is open over the trachea and can be pulled off if inadvertently gripped). These garments have been shown to gently facilitate natural response mechanisms in several small neck muscles and tendons (the Omohyoids), which are universally present in mammals and birds.

The physiologies imparted by these Omohyoids (and further facilitated by these garments) merely approximate natural physiologies, which occur when individuals lie in the prone, or supine position, and are also comparable to the simple act of yawning (which has been shown to collapse the jugulars). The Device will intentionally deliver an exacting, but gentle compression to the Omohyoid muscles in the neck allowing these muscles to optimize blood outflow of the neck vasculature. In the upright position (without the collar), the resultant vascular blood column siphons volume out of the neck, rapidly, creating a negative pressure on the cranium and resulting in a slight "under filling" and "sloshability" inside the skull.

The Omohyoid muscle raises the volume of the intracranial space by design. The Device does not contain any inherently rigid structures in its design. Similarly, neckties circumnavigate the neck, and safely raise intracranial pressure and volume comparable to the Device. The Device is manufactured of a soft rubber similar material and should be barely noticeable to the wearer. Careful MRI studies have confirmed an increase in blood volume in the brain but have also shown that there is no significant change in brain blood flow pattern with wearing a "tight necktie" (Rafferty, Quinn et al. 2010).

Evaluation of monitored vital signs, biomechanics, cardiorespiratory capacity, postural control, dynamic stabilization, reactive index, concentration and cognition, memory, strength

and power in a population of athletes showed no statistically significant adverse effect of wearing a mild jugular vein compressive neck collar compared to a sham arm band.(Myer, Edwards et al. 2013) Cumulatively, the pre and post safety measures indicate that neurologic parameters of executive function, eye-hand coordination, balance, memory, strength, power, oxygen uptake, cardio-metabolic measure and reaction times were unchanged following two hours of physical testing wearing the collar prototype.(Barber Foss, Clark et al. 2017, DiCesare, Barber Foss et al. 2017, Thomas, Edwards et al. 2017) Acceptance of the compression collar was not different in physiological biomarker response to the non-collared condition during maximal oxygen uptake and maximum effort power testing

Considering the above mentioned findings on jugular compression, this device can be considered not to meet the definition of a "significant risk device," as that term is defined in 21 C.F.R. § 812.3(m).

MR Imaging of the Brain: The risk the magnetic fields and the strengths, and radio waves is vanishingly small. Some patients can experience anxiety from the confined space of the magnet's bore. Therefore people with known claustrophobic tendencies will be excluded from the study. Another minor concern when using magnetic resonance technology is the noise the magnet makes when collecting data. Noise abatement measures are used; headphones and music with a selection of music options. Ferrous implants and or piercings can be affected in the magnetic field. Therefore participants will be advised to remove these and or scanned with a metal detector to screen for such objects.

Our colleague's previous experience with MRI experiments (who will be present and has a decade of experience with this technology) has provided confidence that there should be no psychological, physical, legal, or social risks involved with MRI experiments in general, though participants may be anxious about the scan, possibly causing them slight stress. The MRI scanning will be performed using the 3 T Siemens Trio MRI scanner. MRI does not involve ionizing radiation and scans up to 8 T are considered as non-significant risk. The risks common to all MRI scans can be described as: (1) ferromagnetic objects introduced into the magnetic field, (2) confinement in the scanner bore, (3) radio-frequency (RF) heat deposition in tissue which is monitored by the system to conform with FDA guidelines, and (4) acoustic noise. These risks are addressed below: Participants are allowed to communicate with the MR operator via an always-on, two-way intercom at any time. In addition, the participants have a hand-held air ball to squeeze in the event that they elect to be removed from the magnet immediately. Thus, the participants have control over their presence in the magnet, which in turn tends to minimize feelings of claustrophobia.

The MR imaging will be initially reviewed by a licensed radiologist just as it would be if it were being used as part of routine medical care. There is a possibility that while reviewing MR images we may see an abnormality that we did not expect to see in this study. In this event, we will notify the participant's legal representative (or participant is 18 years or older) if we see such an incidental finding. Depending on the type of incidental finding, we may contact the participant by mail or by phone. A member of the research team will discuss the incidental finding with the legal representative (or participant if over the age of 18 years). If the participant chooses, we will give information about this incidental finding to their primary

doctor or we will refer them to an appropriate doctor for further evaluation. The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study.

Data Storage. There is also a minimal risk that the data collected for each participant may be viewed by individuals outside the research team. The risk that confidential data may be viewed is relevant for both the written forms and electronic databases. Precautions, such as password-protected computers, locked cabinets and coded identification numbers, are in place to minimize this risk.

Adverse Events. During the course of the investigation, injuries consistent with the sports being monitored are expected to occur (E.g. concussion, musculoskeletal injury, bone fractures). Care of all injuries will follow standard of care as directed by the team's athletic trainer and/or the participants treating physician. CCHMC will not be responsible for the medical treatment of any injuries that are not directly related to wear of the Q-collar device. In the case of an adverse event that is determined to be directly related to the wear of the Q-collar during competitive play, the principal investigator will report such event to Cincinnati Children's Hospital Medical Center IRB as any future funding organizations in a manner consistent with the requirements of each organization. As described in the consent, if a participant believes they have sustained an injury as a result of the study then they are instructed to contact the principal investigator or director of social services who in turn will then contact CCHMC IRB and necessary funding institutions, as aforementioned. If a participant sustains an injury during testing they will be referred to the most appropriate medical facility or seek medical attention by the physician/medical specialist of their choice.

(13) RISK/BENEFIT ANALYSIS:

Participants will be approached for participation via the appropriate method. The purpose and the study protocol will be fully explained in conversation and with the informed consent process.

On the day of the study, the investigators will confirm that the volunteer participant has no health impairment as outlined in the exclusion criteria. Time will be taken to repeat the aims of the study, test protocol, and to answer any remaining questions posed by the participant.
The methods described in this protocol have been used extensively in previous testing in the laboratory. During previous testing, there have been no reported injuries, adverse events or complications. Additionally, the investigators have considered potential risk for injury and have taken additional steps, described in the protocol, to minimize these risks.

A study participant may be withdrawn from the investigation if they demonstrate repeated alteration in their proper football tackling technique, such as adoption of spearing tackling tendencies. Subject participation will also be halted should an adverse event while wearing the collar, such as syncope, occur. Any adverse events will be immediately reported. The safety officer will evaluate all adverse events and will determine if early stopping of the study due to safety concerns is warranted. Given the study design and sample, we do not deem futility or efficacy stopping rules are warranted.

(14) DATA SAFETY & MONITORING:

The Safety Officer will act in an advisory capacity to the Principal Investigator (PI) to monitor patient safety and progress for the clinical trial, and will be the contact person for severe adverse event reporting.

The Safety Officer's responsibilities are to:

- review the research protocol, informed consent documents and plans for data safety and monitoring;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- review study performance, make recommendations and assist in the resolution of problems reported by the PI;
- protect the safety of the study participants;
- report to the PI on the safety and progress of the trial;
- make recommendations to the PI concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- ensure the confidentiality of the trial data and the results of monitoring; and, assist the PI by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The Safety Officer and PI will hold meetings to review the data safety, the first of which will be held prior to initiation of the trial to discuss the protocol, approve the commencement of the trial, and approve the plans for monitoring the study. Meetings with the safety officer will be determined by the PI and will be closed to the public because of confidentiality considerations. An emergency meeting may be called at any time by the Safety Officer, or by the PI, should questions of participant safety arise.

This research study involves only minimal risk for participants (see Risk/Benefit Analysis section (15)). Further assurances regarding participant safety and protection of private and confidential participant information have been outlined in the Potential Risks, Discomforts, Inconveniences and Precautions section (14), the Privacy section (18) and the Confidentiality section (19). If during the, preliminary analyses the research team identifies strong evidence of harm from the Q-collar device the study will be stopped immediately.

(15) PRIVACY AND CONFIDENTIALITY:

The participant has the right to privacy. The investigators will protect participant privacy to the extent allowed by law. All facts about this study that can describe a participant's name will be kept private. Results of the study will be summarized regarding age, etc. but the investigators will take every precaution necessary to keep names private.

To maintain the privacy information of study participants, only pertinent research personnel will have access to participant information. Research personnel are employees of CCHMC and have been trained in human participants research and HIPAA compliance. To further insure privacy, all data will be analyzed and tracked using a coded identification number that does not use identifiable personal information. Personal information and identifiers will be securely recorded and filed by the administrative assistant. The data will be encrypted with a password and stored on a personal computer and backed up on a network drive. The participant identification code will be used on all data questionnaires.

The results of this study will be kept confidential. No participant identification will be made public record in any form unless the participant gives his or her expressed written permission of release of participant's name, photograph or likeness captured on video. The investigators will be available for any questions that may arise.

To further insure confidentiality, only pertinent research personnel will have access to participant information. Research personnel are employees of CCHMC and have been trained in human subjects research and HIPAA compliance.

(16) COST OF PARTICIPATION:

Participants will endure no costs other than time and effort in participating in this study. Insurance will not be billed for any of the tests associated with this study.

(17) PAYMENT FOR PARTICIPATION:

Participants will be compensated for their time and effort in participating in this study. They will receive a $50 Clincard Mastercard® gift card for completing the first testing session and a $100 Clincard Mastercard® gift card for completing the final testing session. Participants who sustain a clinically diagnosed concussion will also receive $50 for each completed session following new concussion diagnosis.

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