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ORIGINAL RESEARCH ARTICLE

Effect of Routine Sport Participation on Short-Term Clinical Neurological Outcomes: A Comparison of Non-Contact, Contact, and Collision Sport Athletes

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Abstract

Objectives To compare pre-season to post-season changes on a battery of clinical neurological outcome measures between non-contact, contact, and collision sport athletes over multiple seasons of play.

Methods 244 high school and collegiate athletes participating in multiple non-contact, contact, and collision sports completed standardized annual pre-season and post-season assessments over 1–4 years. Pre/post-season changes in 10 outcome measures assessing concussion symptoms, neurocognitive performance, and balance were compared between the groups using linear mixed models.

Results Small, but statistically significant overall pre/post-season change differences were present between the groups for Axon computerized neurocognitive test processing speed, attention, and working memory speed scores (Axon-PS, Axon-Att, Axon-WMS), as well as Balance Error Scoring System (BESS) total score. Small seasonal declines not exceeding reliable-change thresholds were observed in the collision sport group relative to the contact and non-contact groups for Axon-PS and Axon-Att scores. The collision and contact sport groups demonstrated less pre-/post-season improvement than the non-contact sport group for Axon-WMA and BESS, with less BESS improvement also observed in the collision sport group relative to the contact sport group. Overall, longitudinal performance on all 10 outcome measures remained stable in all 3 groups over 4 years.

Conclusion Our findings do not necessarily support the notion that participation in sports associated with exposure to repetitive head impacts has clinically meaningful cumulative effects over the course of a season, nor over four consecutive seasons in high school and collegiate athletes.

1 Introduction

Sport participation rates continue to rise, with over 7.8 million high school and 490,000 collegiate athletes competing annually in the US [1, 2]. While sport participation is associated with many physical, psychological, and social benefits, these benefits come at the potential risk for sustaining athletic injuries. Recently, much attention has been paid to the potential adverse effects of sport-related concussion (SRC) on athletes' short- and long-term neurological health. Many have also questioned whether repetitive head impacts (RHIs) not causing concussion that are sustained during sport may also have adverse neurological effects.

This question gained attention in 2014 when Talavage et al. first reported a series of non-concussed high school football athletes who demonstrated measurable cognitive decline on computerized neurocognitive testing as well as neurophysiological changes on functional magnetic resonance imaging (fMRI) over a high school football season [3]. In follow-up studies, this group reported the degree of fMRI-based neurophysiological change over a football season was positively associated with the number of head impacts sustained [4]. Furthermore, athletes with 50 or more head impacts per week were more likely to exhibit neurophysiological changes on fMRI persisting to the post-season [5].

Other studies also support an association between sport-associated RHIs and various outcome measures. The majority have utilized one or more advanced MRI modalities and have identified associations between RHI exposure and changes on resting state fMRI [6–10], diffusion tensor or

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Key Points

This study is the first to longitudinally compare the effect of participation in sports with varying exposure to repetitive head impacts on a battery of clinical outcome measures over multiple seasons of play.

We identified small magnitude, but statistically significant, pre/post-season change differences between non-contact, contact, and collision sport athletes for 3 measures of neurocognitive performance and one measure of balance, with greater decline/less improvement observed in the collision sport group.

Overall performance over the course of four seasons remained stable or demonstrated a trend of improvement across all three athlete groups for all outcome measures.

These findings will have an impact on clinical practice by providing sports medicine providers with new knowledge to inform discussions with athletes and their families regarding the relative risks and benefits of participation in sports associated with repetitive head impact exposure.

diffusion kurtosis MRI [10–20], susceptibility-weighted and arterial spin-labeled MRI [9], or MR spectroscopy [10, 21, 22]. Other studies have reported associations between RHI exposure and changes in non-imaging-based biomarkers such as serum s100B and P3b response amplitudes [23, 24]. Collectively, these studies suggest that cumulative exposure to RHIs may have microstructural and functional effects on athletes' brains. However, the clinical relevance of these imaging and biomarker findings remains unclear.

Studies investigating the effects of RHI exposure on cognition and other clinical outcomes have yielded null or mixed results. The most comprehensive of these assessed pre/post-season changes in a battery of five clinical assessment measures over a single collegiate football season [25]. That study found small but statistically significant improvements in Balance Error Scoring System (BESS) total and Sensory Organization Test (SOT) composite scores, as well as increased total number of symptoms reported on the Graded Symptom Checklist (GSC), felt not to be clinically significant. No changes were identified in Automated Neuropsychological Assessment Metrics (ANAM) outcomes, total Standardized Assessment of Concussion (SAC) score, or Graded Symptom Checklist (GSC) symptom severity. Six additional studies assessed RHI effects on cognition using the ImPACT computerized neurocognitive test (CNT) and/or other cognitive assessment measures in various athlete populations [5, 11, 19, 26–28]. While most identified potential adverse exposure-related cognitive effects in one or more outcomes, effect magnitudes were typically small, and detrimental findings tended to be outnumbered by non-significant results. Two additional studies investigated the effects of one season of collegiate-level collision sport participation on postural stability with mixed results [29, 30]. Finally, one study identified increased (worse) near-point convergence (NPC) over a football season in athletes sustaining higher impact counts, with return to baseline at 3-weeks post-season [31], while a separate study identified declines in visual motor control performance over the course of one lacrosse season, without declines in visual reaction time [32]. A recent formative review concluded that any effect of RHI exposure is likely to be small or nonexistent and that sport-associated RHIs have not been shown to cause significant clinical effects [33].

This expanding body of research has fueled concern over potential adverse effects of cumulative RHI exposure in athletes. However, these results must be interpreted with caution. The clinical relevance of advanced neuroimaging and other concussion-related biomarkers remains unclear given that such changes may reflect different microscopic processes at different time points [34, 35] and similar changes can be observed in diverse settings like reasoning and skill training [36, 37]. Furthermore, the relatively small clinical changes typically fall within reliable-change thresholds. With some exceptions, the majority of investigations have assessed small cohorts of athletes, often without controls for comparison. Lastly, few studies have included follow-up beyond one season. As such, the duration of observed effects remains unclear. Additional research addressing the potential cumulative effects of sport-associated RHI exposure in athletes is needed.

To address this need, the National Sport Concussion Outcomes Study (NSCOS) was initiated in the Fall of 2012 as a multi-site prospective observational study in youth, high school, and collegiate athletes. Collegiate NSCOS activities have since been integrated into the larger National Collegiate Athletic Association-Department of Defense Concussion Assessment Research and Education (NCAA-DOD CARE) Consortium Study, which continues at this time [38]. The present analysis longitudinally compares pre-season baseline to post-season performance changes on a battery of clinical neurological outcome measures between non-contact, contact, and collision sport athletes over multiple seasons of play.

2 Methods

2.1 Participants

Two-hundred-forty-four athletes (36.1% female) competing in multiple sports at the high school (41.8%) and collegiate

(58.2%) levels of play were included in this analysis. Participants from a parent population of 962 NSCOS athletes assessed between 2012 and 2016 at 3 institutions were analyzed if complete data were available for at least one primary study outcome (described below) at both the pre-season and post-season assessment time points of the same athletic year. Participants with missing data for any of 8 key covariates controlled for in the statistical models (also described below) were excluded. This study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki. All participants provided informed written consent, or assent with parent/guardian consent for minors, using local Institutional Review Board-approved documents.

2.2 NSCOS Protocol Overview

Participants completed a standardized pre-season baseline assessment prior to each season, as well as a post-season assessment within 1 month of their last practice or competition (Table 1). Data were collected by trained research personnel at each site. Participants sustaining a concussion during the study period also completed a series of standardized after-injury assessments, which are not reported in the current analysis.

2.3 Study Measures

A baseline questionnaire was completed upon enrollment including demographics, sport participation history, academic history, and medical history, emphasizing sport- and non-sport-related concussions and neurological comorbidities. All other measures were established assessment tools, previously described in detail. Briefly, self-reported concussion symptoms were assessed using the Sport Concussion Assessment Tool (SCAT) 2 Symptom Checklist, yielding both a total symptom number and a symptom severity score [39]. Psychological distress was assessed using the Brief Symptom Inventory (BSI)-18, which yields depression, anxiety, and somatization scores [40]. The 5-item Satisfaction With Life Scale (SWLS) was used to assess participants' quality of life [41]. Mental status was assessed using the Standardized Assessment of Concussion (SAC), evaluating orientation, memory, concentration, and delayed recall [42, 43]. Clinical reaction time (RT_{clin}) was assessed using a standardized ruler-drop test [44, 45]. Cognition was assessed with different computerized neurocognitive assessment tools (CNTs) at each site: Axon (CogState) [46], ImPACT [47], or CNS Vital Signs [48]. Computerized testing was administered to athletes in small groups under the supervision of a study team member. Less than 10% of computerized assessments were completed using ImPACT or CNS Vital Signs, so only Axon results are presented in this report. The Axon CNT reports standardized scores for processing speed (PS), attention (Att), learning (Learn), working memory speed (WMS), and working memory accuracy (WMA). Lastly, postural stability was assessed using the Balance Error Scoring System (BESS) [49]. This manuscript classifies these outcomes as measures of concussion symptoms (SCAT2 total symptoms and symptom severity score), neurocognitive performance (SAC, RT_{clin}, and Axon results), and balance (BESS).

2.4 Data Analysis

The primary independent variable was level of contact associated with participants' primary sport, classified as non-contact, contact, or collision based on Rice's categorization [50]. Sports with infrequent or inadvertent contact were classified as "non-contact;" sports with routine low-force contact were classified as "contact;" sports with frequent, purposeful hits or collisions at high levels of force were classified as "collision" (Fig. 1). The symptom, neurocognitive, and balance outcomes (Table 1) at each pre-season baseline and post-season time point were the study's primary outcomes, with a focus on pre/post-season changes. Other covariates considered in the statistical models included site, sex, level-of-play (high school vs. collegiate), study year (Y1–Y4), baseline BSI-18 and SWLS scores, and prior self-reported history of concussion, migraine headache, and attention deficit disorder/attention deficit-hyperactivity disorder. Each athlete's year of enrollment, rather than the study's first calendar year, was considered their Y1. As such, all athletes enrolled in the study for any given study year must also have been enrolled for each previous year of the study as well.

All analyses were conducted using R statistical software. Prior to analysis, non-normally distributed variables were log-transformed to approximate normality. Separate independent linear mixed-effect models were used to analyze each of the 10 primary outcomes (Table 1) in the entire cohort of athletes, including those who sustained concussions during the study period. Initial mixed models included level of contact, as well as each of the above covariates and all potential interaction terms. Automated model selection was then performed using the REML package in R to minimize the Akaike Information Criterion, leaving covariates with significant effects and significant two-way interactions between covariates in each final model. Pre/post-season changes were compared between the contact-level groups by assessing the sport group–time point interaction effects to determine whether pre-season to post-season changes in the outcome measures differed between the non-contact, contact, and collision sport groups. Please refer to Supplement 1 for additional statistical methodological detail.

Table 1 Study measures collected at each data collection time point

Baseline assessment	Post-season assessment
Demographics	
Sport participation, academic, and medical history	
BSI-18	
SWLS	
SCAT-2 Symptom Checklist[1,2]	*SCAT-2 Symptom Checklist*[1,2]
Total Symptom Number (0–22)	Total Symptom Number (0–22)
Symptom Severity Score (0–132)	Symptom Severity Score (0–132)
SAC[1,2]	*SAC*[1,2]
Total SAC Score (30–0)	Total SAC Score (30–0)
Clinical RT[1,3]	*Clinical RT*[1,3]
Mean RTclin (in ms)	Mean RTclin (in ms)
CNT[1,4]	*CNT*[1,4]
Axon Processing Speed Standardized Score	Axon Processing Speed Standardized Score
Axon Attention Standardized Score	Axon Attention Standardized Score
Axon Learning Standardized Score	Axon Learning Standardized Score
Axon Working Memory Speed Standardized Score	Axon Working Memory Speed Standardized Score
Axon Working Memory Accuracy Standardized Score	Axon Working Memory Accuracy Standardized Score
BESS[1,2]	*BESS*[1,2]
Total BESS Score (0–60)	Total BESS Score (0–60)

[1]Designates a primary study outcome measure

[2]Score range reported as (Best performance−worst performance)

[3]Lower RTclin values represent faster/better performance

[4]Only Axon CNT results are presented in this report; each Axon Standardized Score is based on a scale with mean 100, standard deviation 10, and higher scores representing better performance

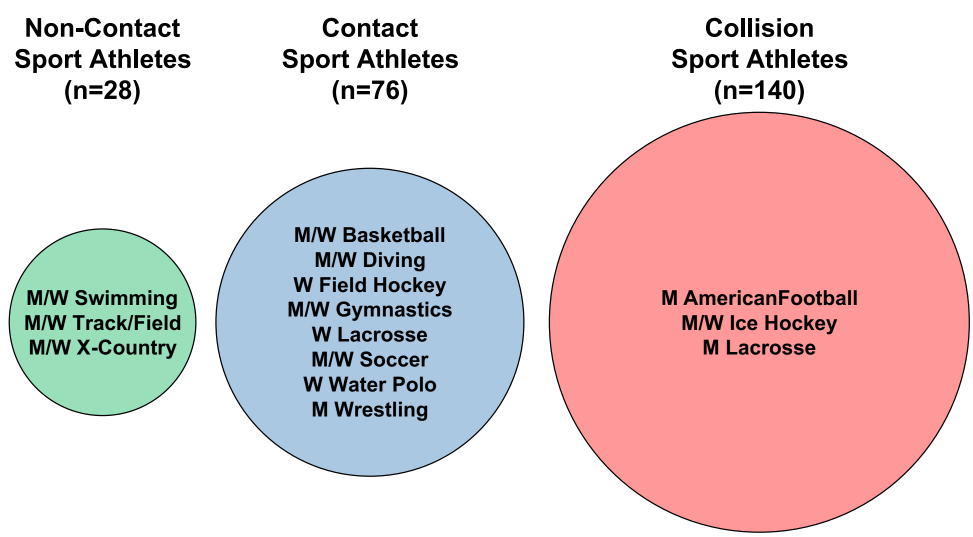


Fig. 1 Composition of non-contact, contact, and collision sport groups. Circle areas are proportional to the number of participants in each group

3 Results

Baseline characteristics of each group are presented in Table 2. Significant baseline differences were present between groups for sex, level-of-play, baseline BSI Depression and Somatization scores, and prior concussion history.

Overall model-predicted baseline, post-season, and change values for each outcome, as well all covariates

Table 2 Baseline characteristics of the study population

Feature	Non-contact sport group	Contact sport group	Collision sport group	Significance
Number of athletes per study year	28 (Y1), 25 (Y2), 19 (Y3), 20 (Y4)	76 (Y1), 62 (Y2), 50 (Y3), 28 (Y4)	140 (Y1), 87 (Y2), 32 (Y3), 26 (Y4)	N/A
Age (years)	18.00 (0.47)	18.10 (0.61)	16.40 (1.36)	$P=0.236$
Sex (% female)	53.6%	70.4%	25.8%	*P < 0.001*
Level of play (% collegiate)	100%	98.8%	38.6%	*P < 0.001*
Baseline BSI Depression Score (% abnormal)[1]	7.1%	1.3%	0.7%	*P = 0.048*
Baseline BSI Anxiety Score (% abnormal)[1]	7.1%	2.6%	0.7%	$P=0.082$
Baseline BSI Somatization Score (% abnormal)[1]	14.2%	10.5%	2.1%	*P = 0.008*
Baseline SWLS Score	29.0 (5.12)	30.2 (3.86)	29.9 (4.57)	$P=0.065$
Prior history of concussion (%)	25.0%	35.5%	48.5%	*P = 0.028*
Prior history of migraine headache (%)[2]	14.3%	18.4%	12.1%	$P=0.457$
Prior history of ADD/ADHD (%)	10.7%	5.3%	3.6%	$P=0.279$

All values are mean (SD) unless otherwise specified

[1]BSI cutoff values corresponding with T-Scores ≥ 63 were used: Depression Score > 7 (male), > 9 (female); Anxiety Score 7 (male), > 9 (female); Somatization Score > 6 (male and female) [51]

[2]Based on positive self-report or positive response to the ID Migraine Questionnaire [52]

included in each model, are presented in Table 3, with raw data represented visually in Fig. 2. There were no between-group differences in pre/post-season change values for either concussion symptom measure. Small, but statistically significant between-group pre/post-season change differences were present for 3 neurocognitive outcomes. The pre/post-season decline in Axon-PS Scores in the collision sport group differed from the increases in the non-contact ($p<0.001$) and contact sport ($p<0.001$) groups. The pre/post-season decline in Axon-Att Scores in the collision sport group differed from the increases in the non-contact ($p<0.001$) and contact sport ($p<0.001$) groups. While, Axon-WMS Scores increased from baseline to post-season in all three groups, the larger increase in the non-contact sport group was significantly greater than the smaller increases in the contact ($p=0.038$) and collision sport ($p=0.019$) groups. All three groups had pre/post-season improvements in balance, with small but significantly different magnitudes change between the groups. BESS total score improvement was greatest in the non-contact sport group, followed by the contact sport group, and the collision sport group ($p=0.003$; $p<0.001$; $p=0.017$ for non-contact/contact, non-contact/collision, and contact/collision comparisons, respectively).

Study year was not a significant covariate in any of the 10 outcome models. While there was no significant time-effect for any outcome measure, a small degree of progressive improvement was observed in all 3 groups for some outcomes (e.g., SAC, RTclin, Axon-Learn, Axon-WMS, BESS), suggesting the possibility of a small practice effect. Greater variation between successive time points is observed in the non-contact sport group compared to the contact and collision sport groups for some outcomes (e.g., SCAT2 symptom number and severity score; Axon-Learn, Axon-WMS), likely attributable to a more pronounced effect of outlier values in the smaller non-contact sport group. Trends in raw concussion symptom, neurocognitive, and balance-related primary outcomes over the 4-year study period are illustrated graphically in Fig. 3.

4 Discussion

In this study, we observed small but statistically significant differences in pre/post-season change for 4 of 10 clinical outcome measures between collision, contact, and non-contact sport athletes. Three of these outcomes were neurocognitive measures assessing speed (Axon-PS, i.e., simple reaction time; Axon-Att, i.e., discriminative choice reaction time; Axon-WMS, i.e., one-back reaction time), while the fourth was a test of balance (BESS). Post-season performance improved relative to baseline for most of these group-outcome comparisons, except for declines in Axon simple and choice reaction time in the collision sport group. For Axon simple reaction time, the magnitude of decline in the collision sport group was less than the 87.5% confidence change score, as defined in the CARE Consortium cohort, [53] while the decline in Axon choice reaction time was less than the 75% confidence change score. In the cases of Axon one-back reaction time and balance, the between-group discrepancies likely represented only differential practice effects, with all three groups still demonstrating overall improvement from pre-season to post-season. Furthermore, the longitudinal findings are noteworthy in that the small pre/post-season declines observed for Axon simple and

Table 3 Primary study outcomes by time point and study group

Outcome	Group (annual n, Y1-Y4)	Pre-season value[1]	Post-season value[1]	Change value[1]	Non vs. Con[2] significance[4]	Non vs. Col[2] significance[4]	Con vs Col[2] significance[4]	Model[3]
SCAT2: Total Symptom Number	Non-contact (28, 25, 19, 20)	3.86	4.00	(*0.14*)	0.788	0.978	0.123	Mig + ADHD + Prior + Sex + Anx
	Contact (76, 62, 50, 28)	3.69	3.69	0.00				
	Collision (137, 87, 32, 26)	3.03	3.39	(*0.36*)				
SCAT 2: Symptom Severity Score	Non-contact (28, 25, 19, 20)	7.06	10.80	(*3.74*)	0.919	0.509	0.154	Sex + Mig + Somat + Anx + GSI
	Contact (76, 62, 50, 28)	6.64	10.18	(*3.54*)				
	Collision (137, 87, 32, 26)	5.60	8.65	(*3.06*)				
SAC Total Score	Non-contact (23, 22, 19, 20)	28.07	27.90	(*− 0.17*)	0.067	0.095	0.742	Sex + Sport:Sex
	Contact (76, 62, 50, 28)	27.32	27.73	**0.41***				
	Collision (137, 87, 32, 25)	27.47	27.82	**0.34***				
Mean Clinical RT (ms)	Non-contact (28, 25, 19, 20)	191.93	186.74	− 5.18	0.231	0.963	0.108	Sex + Somat + Sport:Sex
	Contact (76, 62, 50, 28)	194.63	185.56	**− 9.08****				
	Collision (137, 87, 32, 26)	197.04	191.71	**− 5.33***				
AXON: Processing Speed	Non-contact (20, 18, 17, 15)	101.92	103.37	1.45	0.604	**< 0.001**	**< 0.001**	Sex + Level + Sport:Level
	Contact (76, 61, 50, 28)	103.76	104.67	0.91				
	Collision (132, 87, 31, 25)	103.77	100.48	**(*− 3.30*)****				
AXON: Attention	Non-contact (20, 18, 17, 15)	103.14	104.13	0.99	0.535	**< 0.001**	**< 0.001**	
	Contact (76, 61, 50, 28)	105.91	106.36	0.44				
	Collision (132, 87, 31, 25)	106.75	104.25	**(*− 2.50*)****				
AXON: Learning	Non-contact (20, 18, 17, 15)	105.68	105.99	0.31	0.194	0.888	0.062	Level + Prior
	Contact (76, 61, 50, 28)	104.26	106.99	**2.73***				
	Collision (132, 87, 31, 25)	104.69	105.26	0.57				
AXON: Working Memory Speed	Non-contact (20, 18, 17, 15)	100.28	102.98	**2.70***	**0.038**	**0.019**	0.704	Sex
	Contact (76, 61, 50, 28)	104.15	104.86	0.70				
	Collision (132, 87, 31, 25)	103.24	103.74	0.48				
AXON: Working Memory-Accuracy	Non-contact (20, 18, 17, 15)	99.90	101.53	1.64	0.909	0.935	0.959	Sex + Somat
	Contact (76, 61, 50, 28)	100.25	101.71	**1.46***				
	Collision (132, 87, 31, 25)	99.52	101.03	**1.51***				
BESS Total Score	Non-contact (28, 25, 19, 20)	15.83	10.52	**− 5.30****	**0.003**	**< 0.001**	**0.017**	Sex + Mig + ADHD + Sport:ADHD + Sport:Mig
	Contact (76, 62, 50, 28)	14.76	12.24	**− 2.43****				
	Collision (137, 87, 32, 26)	13.79	13.59	− 0.20				

[1]Overall model-predicted baseline, post-season, and change values for each outcome. Change values are calculated as the post-season value minus the pre-season value for each outcome. Declines/worse performance from pre-season to post-season are highlighted in (italics). Statistically significant within-group changes are highlighted in bold: *designates $p < 0.05$, **designates $p < 0.001$

[2]Non = non-contact sport group; Con = contact sport group; Col = collision sport group

[3]List of additional covariates retained in each statistical model. Note that all models include sport group (non-contact, contact, and collision), time point (pre-season, post-season), and sport group-by-time point interaction terms, so these are not listed individually for efficiency. Anx = abnormal Anxiety response on baseline BSI-18; ADHD = history of ADD/ADHD; GSI = abnormal Global Severity Index on baseline BSI-18; Level = level of play (high school, collegiate); Mig = history of migraine headache; Prior = prior history of concussion; Sex = biological sex; Somat = abnormal somatization response on baseline BSI-18; Sport = sport group. Interaction terms are indicated by ":". Study year (Y1-Y4), Depression response on BSI-18, and SWLS score were not significant covariates in any of the models

[4]*P* values reflect the significance of the group-by-time interaction term for each outcome, with statistically significant results highlighted in bold

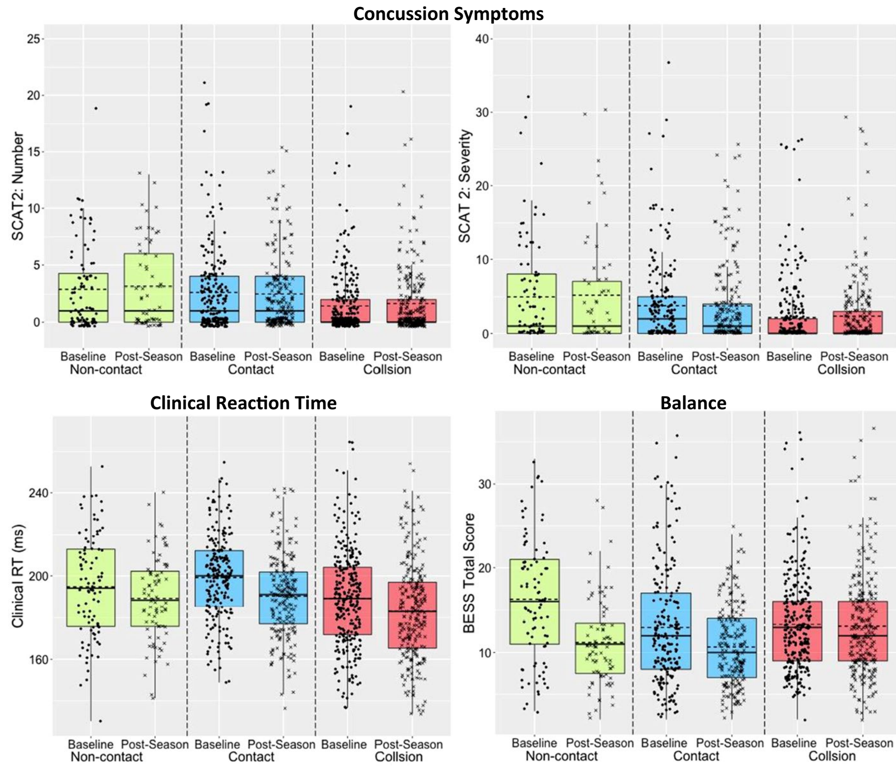


Fig. 2 Boxplots presenting overall raw baseline and post-season results for each outcome by sport group. Solid lines represent median values; dashed lines represent mean values; boxes represent interquartile ranges; whiskers represent 1.5× the interquartile values. Individual baseline observations are represented by dots while post-season observations are represented by x's

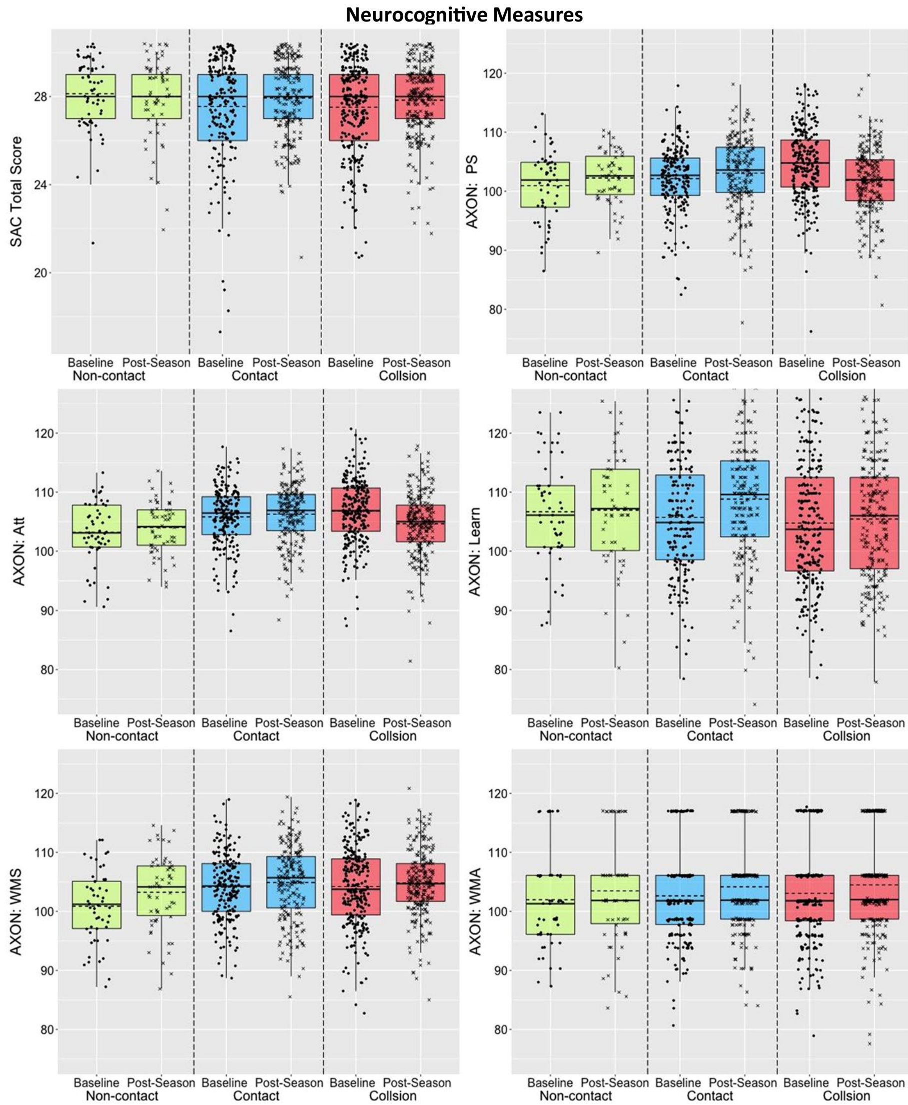
choice reaction time performance tended to improve by the subsequent pre-season baseline assessment and none of the outcomes demonstrated significant changes over the 4-year study period (Fig. 3).

These results build upon the existing literature addressing the potential cumulative effects of sport-associated RHI exposure in athletes. Several previous studies have compared a contact or collision sport cohort to a non-contact control group, but only one previous study using multi-modal advanced neuroimaging has assessed exposure to sports across a continuum of RHI exposure by comparing collision, contact, and non-contact sport athletes [10]. This study is therefore the first to employ such a design to assess the effects of sport participation stratified by three levels of RHI exposure on a battery of clinical outcomes. Furthermore, this is the first study to longitudinally monitor such effects in individual athletes over four seasons, thereby providing novel insight into the duration of observed changes.

The direction of each statistically significant between group difference in our study did occur such that the most favorable pre/-post-season trend (i.e., greatest improvement or least decline) was observed in the non-contact sport group and the least favorable (i.e., greatest decline or least improvement) in the collision sport group. While many different clinical, neuroimaging, electrophysiological, and other concussion-related outcomes have been assessed in previous studies, our findings are broadly consistent with the existing body of literature addressing the potential cumulative effects of sport-associated RHI exposure in athletes. Specifically, significant between-group pre/post-season change differences were present only for some outcomes (i.e., Axon simple, choice, and one-back reaction time; BESS), with the significant Axon simple and choice reaction time declines being small in magnitude and exceeding only low-certainty change score thresholds. For directly comparable outcomes, our present findings share some similarities with previous work. For example, the absence of a sport exposure effect on concussion symptoms and SAC scores is similar to Gysland et al's findings [25]. In addition, the observed pre/post-season BESS improvement is also consistent with Gysland et al. [19], while the smaller amount of pre/post-season BESS improvement in our collision sport group is loosely consistent with Miyashita et al.'s [29] finding of a RHI effect on BESS. We note that although other studies have used the same outcome measures, differences in their design preclude direct comparisons with our present results.

The Axon simple, choice, and one-back reaction time, as well as BESS findings are consistent with previous work suggesting that participation in sports associated with greater exposure to RHIs may have measurable, but clinically insignificant cumulative neurological effects over the course of a season. While the majority of previous studies on this topic have assessed neuroimaging-based measures of brain structure and function, this study adds to the literature speaking to potential effects on clinical measures of cognitive and balance performance and concussion-related

Fig. 2 (continued)



symptoms. The presence of between-group pre/post-season differences raises concern for potential risk to neurocognitive health associated with sport participation that has not traditionally been considered. However, this concern is tempered by the observation that the differences identified for Axon one-back reaction time and BESS still represent improved performance in contact and collision sport athletes over the course of a season. Furthermore, while there were group-level reductions in Axon simple and choice reaction time performance in the collision group, these changes were small in magnitude and could not confidently be considered clinically significant at the level of the individual athlete. Importantly, it is also reassuring to see that both observed pre/post-season declines appear to have improved by the subsequent season's baseline assessment and remained stable over time in those athletes who were followed for more than a single season. While other factors such as normal development and maturation or a learning effect associated with multiple test administrations may also potentially contribute to the observed "off-season" improvements in Axon simple and choice reaction time observed in the collision group, no progressive decline was observed. We note the lower incidence of abnormal BSI-depression scores in the contact and collision sport groups is also reassuring with respect to any potential risks associated with RHI exposure to neurocognitive health (Table 2).

While a strength of this study is its inclusion of male and female athletes competing in multiple sports at both the high school and collegiate levels, a related weakness is the imbalance between the study groups. The majority of the high school athletes in this study participated in collision sports, with no non-contact sport athletes at the high school level. Significant sex differences were also present between the groups. While these discrepancies are incorporated into the statistical analysis, greater balance between the study groups would provide more robust results. Also,

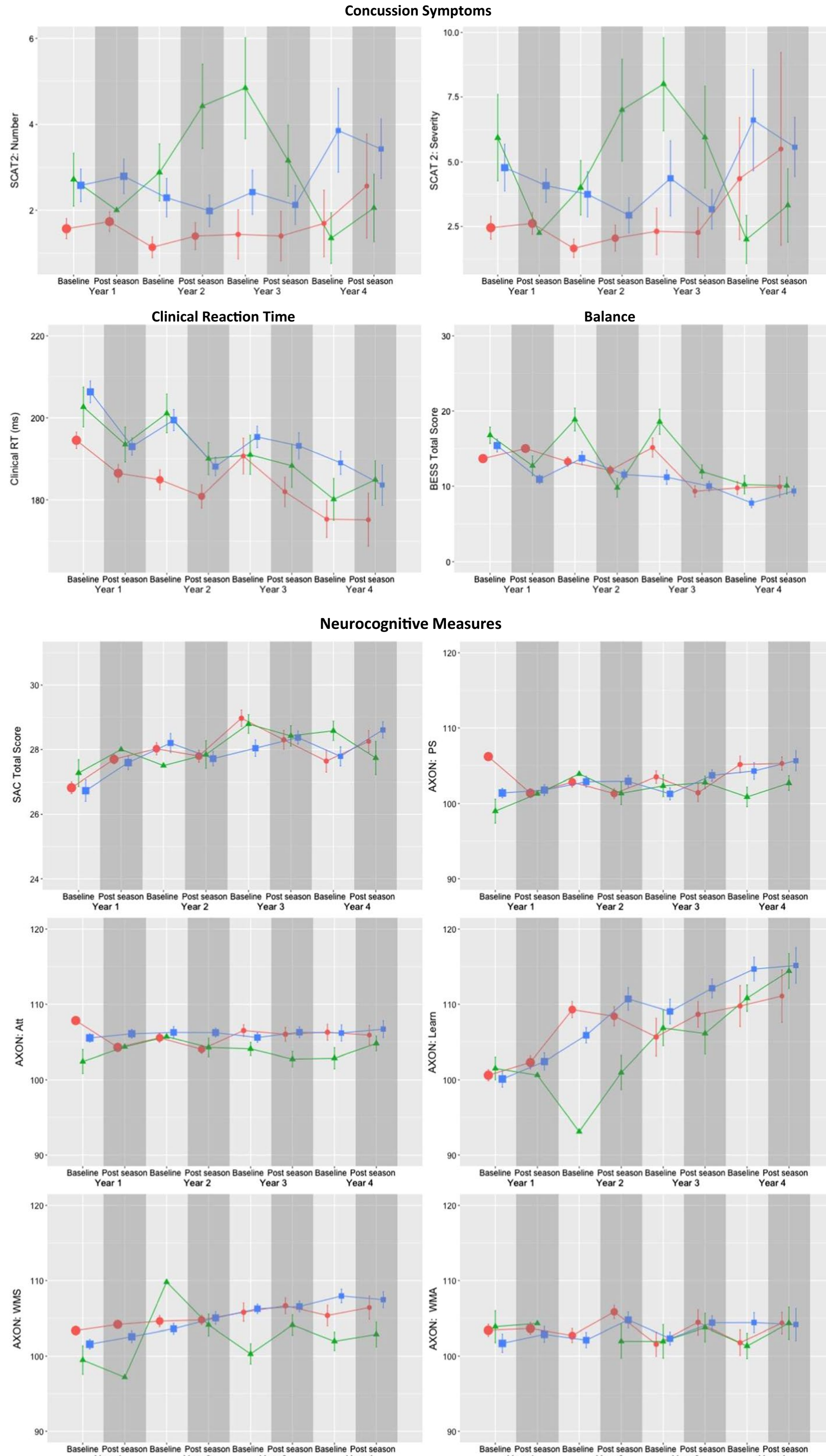


Fig. 3 Line graphs presenting raw mean (SE) results for each outcome at each study time point by sport group. green = non-contact sport group; blue = contact sport group; red = collision sport group. Note, the size of each marker reflects the number of observations in the respective group at that time point

while this study's follow-up period of up to 4 years is a strength of its design, the increasing proportion of missing data with each subsequent study year limits the strength of the longitudinal conclusions. The smaller number of athletes in the non-contact group, in particular, likely contributes to the greater instability observed in this group for some outcome measures over the 4 years of the study (e.g., SCAT2 Symptom Number and Severity Score, Axon memory and one-back reaction time scores; Fig. 3). However, despite the decreasing sample size over study years, the variance for most outcomes remains relatively stable over assessment time points. Additionally, there is no universally agreed-upon system for stratifying contact exposure across sports. We considered the typical frequency, intentionality, and magnitude of contact, as described by Rice [50], to classify each sport as non-contact, contact, or collision but other classification schemes could be considered. Furthermore, while there are expected differences in RHI exposure between the collision, contact, and non-contact sport groups, wearable head impact sensor technology was not employed so the number of RHIs sustained by athletes was not quantified. Such quantification would be a challenge to accomplish across the 14 sports, including 11 non-helmeted and 3 aquatic sports, included in this study. Lastly, other factors such as sleep, caffeine intake, psychological distress, and hydration status that could have potentially influenced the neurocognitive, balance, and symptom outcomes were not controlled for in this study.

While not a design limitation per se, we also note that the primary analyses did not exclude those athletes who sustained concussions during the study period. While this raises the possibility that some observed effects could potentially be attributable to concussion rather than cumulative RHI exposure, we feel this is unlikely. To rule out a potential concussion-effect we conducted a secondary analysis excluding those athletes who sustained concussions during the study period with no meaningful differences in the results. The results of this secondary analysis are available in Supplementary Table 3S accompanying this paper.

5 Conclusion

This study identified small, but measurable short-term effects on cognition and balance differentially associated with participation in noncontact, contact, and collision sports. However, the magnitude of these changes failed to reach thresholds of clinical significance, and did not appear to persist into subsequent seasons. Therefore, our findings do not necessarily support the notion that participation in sports with a potential for accumulation of RHIs has a clinically significant cumulative effect over the course of a season, or over four consecutive seasons in high school and collegiate athletes. Our findings also suggest that collision sport athletes may potentially benefit from an off-season period to allow for resolution of any in-season changes that do occur. While this study adds important information to our understanding of subtle cognitive and balance changes associated with contact/collision sport participation over multiple seasons, additional prospective research over a longer follow-up period remains necessary. Sports medicine providers should continue to assist athletes and their families in weighing the many benefits of participating in sport against the potential risks to help them make the best informed health and sport-participation decisions.

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Compliance with Ethical Standards

This study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki. All participants provided informed written consent (or written assent with parental consent, for minors) prior to participation in this study. This research was approved by the Institutional Review Boards at the University of Michigan, Medical College of Wisconsin, University of California Los Angeles, and University of North Carolina. All sources of funding for this study are listed in the Acknowledgements.

Conflict of Interest: In the previous 36 months and during the project period: Author Eckner has received unrelated research funding from the following: US Department of Health and Human Services, National Institutes of Health, NICHD; Rehabilitation Medicine Scientist Training Program; University of Michigan; Foundation for Physical Medicine and Rehabilitation; ElMindA Ltd; he is co-inventor of US patent 8,657,295 owned by employer University of Michigan; he was a paid grant reviewer for SRA International; he received speaker honoraria from the University of Utah and the American College of Oral and Maxillofacial Surgeons/Canadian Association of Oral and Maxillofacial Surgeons Joint Annual Conference. Author Nelson has received unrelated research funding from the NIH, Advancing a Healthier Wisconsin, Department of Defense, National Collegiate Athletic Association. Author Giza has received unrelated research funding from the following: NIH/NINDS, UCLA Brain Injury Research Center, UCLA Steve Tisch BrainSPORT Program, Easton Clinic for Brain Health; he has received consultant fees from Neural Analytics Inc.; he has been a paid advisory panel member for Highmark Interactive with stock/stock options and an unpaid advisory panel member for the MLS, NBA, US Soccer, and NCAA (travel reimbursement only for MLS and NCAA); he has been a Data Safety Monitoring Board member for LA Biomed

Institute; he has received payment for providing expert medical-legal testimony; he receives book royalties from Wiley Publishing; he has received speaker honoraria for Sports Neurology lectures at multiple academic and medical institutions; he is a clinical consultant to the LA Lakers, NFL-Neurological Care Program, NHL Players Association. Author Guskiewicz has received unrelated research funding from the following: Centers for Disease Control and Prevention; Department of Defense; National Collegiate Athletic Association; National Football League. Authors Wang, Bancroft, Pohorence, Broglio, He, Kutcher, and McCrea declare no conflicts.

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