Rapid #: -27913131

CROSS REF ID: **380427017300018 65**

LENDER: **GZN (University of Wisconsin - Milwaukee) :: Ejournals**

BORROWER: **ORE (Oregon State University) :: Main Library**

TYPE:	Article CC:CCG
JOURNAL TITLE:	Journal of head trauma rehabilitation
USER JOURNAL TITLE:	Journal of Head Trauma Rehabilitation
ARTICLE TITLE:	Research Letter: Concussion-Related General Startle Suppression in Adolescent Athletes
ARTICLE AUTHOR:	Oldham, Jessie R
VOLUME:	40
ISSUE:	1
MONTH:	
YEAR:	2025
PAGES:	E96 - E101
ISSN:	1550-509X
OCLC #:	

Processed by RapidX: 11/12/2026 2:39:09 PM

This material may be protected by copyright law (Title 17 U.S. Code)

J Head Trauma Rehabil
Vol. 40, No. 1, pp. E96–E101
Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Research Letter: Concussion-Related General Startle Suppression in Adolescent Athletes

Jessie R. Oldham, PhD; Angelica DeFalco, BS; Sarah Willwerth, BS; Shannon Nagle, BS; Freya Whittaker, BA; Rebekah Mannix, MD; William P. Meehan, MD; Daniel E. Bradford, PhD

Objectives: We investigated the acoustic startle reflex in recently concussed adolescent athletes compared to healthy controls and those with concussion history (>1 year prior) but no current symptoms. We hypothesized that individuals with recent concussion would have a suppressed startle response compared to healthy controls. **Methods:** We conducted a cross-sectional study on 49 adolescent athletes with a recent concussion (n = 20; age: 14.6 ± 1.6 years; 60% female), a concussion history > 1 year prior (n = 16; age: 14.8 ± 2.0 years; 44% female), and healthy controls (n = 13; age: 13.3 ± 2.8 years; 54% female). We measured the eyeblink of the general startle reflex via electromyography activity of the orbicularis oculi muscle using electrodes placed under the right eye. Measurement sessions included twelve 103 decibel acoustic startle probes ~50 milliseconds in duration delivered ~15-25 seconds apart. The primary dependent variable was mean startle magnitude (μV), and group was the primary independent variable. We used a one-way analysis of variance followed by a Tukey post hoc test to compare mean startle magnitude between groups. **Results:** Mean startle magnitude significantly differed ($F = 5.49$, $P = .007$) among the groups. Mean startle magnitude was significantly suppressed for the concussion ($P = .01$) and concussion history groups ($P = .02$) compared to healthy controls. There was no significant difference between the recent concussion and concussion history groups ($P = 1.00$). **Conclusion:** Our results provide novel evidence for startle suppression in adolescent athletes following concussion. The concussion history group had an attenuated startle response beyond resolution of their recovery, suggesting there may be lingering physiological dysfunction. **Key words:** *adolescents, brain injuries, concussion, psychophysiology*

CONCUSSIONS ARE A SIGNIFICANT health problem, with 20% of adolescents reporting having sustained a concussion.[1] The prevalence of concussion in 10 to 19 year olds increased 71% from 2010 to 2015 with a significant increase among athletes in particular.[1] While most sport-related concussion symptoms resolve within 2 weeks, a true window of physiological recovery has yet to be determined, as current clinical assessments are not sensitive to lingering and difficult-to-detect sensorimotor impairments that may contribute to subsequent musculoskeletal injury risk.[2,3] Robust and reliable psychophysiological measures (eg, acoustic startle)[4] designed to assess functioning of subcortical brain structures critical to sensorimotor functioning have long been used by neural, cognitive, and affective scientists, but have yet

Author Affiliations: *Department of Physical Medicine and Rehabilitation (Dr Oldham), Virginia Commonwealth University School of Medicine, Richmond, Virginia; Department of Psychology (Ms DeFalco), Colorado State University, Fort Collins, Colorado; The Warren Alpert Medical School of Brown University (Ms Willwerth), Providence, Rhode Island; Division of Sports Medicine (Ms Nagle), The Micheli Center for Sports Injury Prevention (Dr Meehan), Waltham, Massachusetts; Division of Sports Medicine (Dr Meehan and Ms Nagle), Division of Emergency Medicine (Dr Mannix), Boston Children's Hospital, Boston, Massachusetts; Oregon State University (Ms Whittaker), Corvallis, Oregon; and School of Psychological Science (Dr Bradford), Oregon State University, Corvallis, Oregon; and Departments of Pediatrics and Orthopedics (Dr Meehan), Departments of Pediatrics and Emergency Medicine (Dr Mannix), Harvard Medical School, Boston, Massachusetts.*

J.R.O. and D.E.B. conceptualized and designed the study, carried out the analyses, drafted the original manuscript, and revised and reviewed the final manuscript. W.P.M. assisted with study conceptualization and design, revised, and reviewed the final manuscript, and critically reviewed the manuscript for intellectual content. R.M., F.W., and A.D. all contributed to the revision and review of the final manuscript and critically reviewed the manuscript for intellectual content. S.W. and S.N. contributed to the structure and organization of the collected data, and revised and reviewed the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This study was supported by the Thrasher Research Fund and the National Institutes of Health (8K12AR084233-03).

W.P.M. receives royalties from (1) ABC-Clio publishing for the sale of his books, Kids, Sports, and Concussion: A guide for coaches and parents, and Concussions; (2) Springer International for the book Head and Neck Injuries in Young Athlete; and (3) Wolters Kluwer for working as an author for UpToDate. His research is funded, in part, by philanthropic support from the National Hockey League Alumni Association through the Corey C. Griffin Pro-Am Tournament and the National Football League. The remaining authors have nothing to declare.

Corresponding Author: *Jessie R. Oldham, PhD, Department of Physical Medicine and Rehabilitation, Virginia Commonwealth University School of Medicine, 1223 E. Marshall St, Richmond, VA 23298 (Jessie.Oldham@vcuhealth.org).*

DOI: 10.1097/HTR.0000000000000979

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

to be directly applied in concussion assessment. These measures may connect more directly to the specific physical structures affected by concussion, thus allowing identification of subtle sensorimotor impairments that likely persist beyond clinical concussion recovery.

Due to its narrow structure and sensitivity to rotational forces, the brainstem is particularly vulnerable to injury from head impact.[5] Further, concussive impact models from professional boxers and football players show that the midbrain region of the brainstem sustains the greatest amount of shearing forces and strains following concussion-threshold impacts.[6] Therefore, a brainstem-mediated reflex is liable to be more affected following concussion than other physiological responses. The acoustic startle response is such a brainstem-mediated whole body flexor reaction to a sudden stimulus (eg, a loud sound burst) that initially presents as an eyeblink.[7] Though startle is a defensive reflex, it can be noninvasively measured in the absence of threat (ie, general startle reactivity) with accessible guidelines on its measurement and analysis.[7] A prominent measure for studying neural mechanisms, general startle reactivity can be noninvasively used to assess the health of brain circuitry, and disruptions in startle are often indications of broader physiological problems with sensorimotor function.[8] This ideally situates the startle reflex as a promising biomarker for assessing the functional integrity of the brainstem post-concussion, providing a potentially valuable tool in both the diagnosis and the ongoing management of head injuries.

Following induced brain injury, rodent models exhibit a suppressed general startle reactivity that persists for weeks postinjury, potentially due to impaired functioning of brainstem circuits.[9] Importantly, startle is a cross-species measure allowing for close translation from animal models to humans.[8] Attenuated startle has been observed in military members with a history of mild traumatic brain injury.[10] However, it is unknown whether this evidence translates to a young human population, as we are not aware of any currently published studies on how concussion may affect acoustic startle in adolescent athletes. Such translation is not only prudent for informing on underlying neurological mechanisms of injury, but also holds promise for close ecological validity given athletes' need to constantly respond to sudden, startling events in sport. The purpose of this study was to test for the first evidence of suppressed general startle reactivity in adolescent athletes with a recent concussion compared to those with and without a concussion history. Based on rodent concussion models and startle's connection to target mechanisms in concussion, we hypothesized that the individuals in the recent concussion group would have a suppressed startle response compared to the healthy controls. To explore the possible persistence of this effect, we also explored whether individuals with concussion history had a suppressed startle reflex compared to healthy controls.

METHODS

Participants

Using a cross-sectional study of adolescent athletes between the ages of 10 and 18, we recruited participants into 3 groups: recent concussion, concussion history (>1 year prior), and healthy controls. Recent concussion participants must have had a diagnosed concussion, based on the most recent consensus guidelines,[11] within the last month and still be presenting to a concussion clinic with symptoms. All recent and concussion history participants were recruited from the same sports medicine concussion clinic. Concussion history and healthy participants were recruited via research flyers posted around the same sports medicine clinic, hospital website, and community recreation sites. The concussion history participants must have had a history of at least one or more medically diagnosed concussion occurring at least 1 year before study enrollment that did not continue to cause any self-reported lingering symptoms. Participants in this group completed a detailed medical history form, at the time of study enrollment, on which they reported the month and year of their prior concussion(s). Healthy controls had no history of medically diagnosed concussion. Only participants with no reported hearing problems were recruited. Exclusion criteria for all participants included current or history of auditory impairment that could interfere with their ability to hear the acoustic startle probes used to elicit the startle response. All enrollment procedures were approved by the respective institutional review board prior to the start of the study, and consent/assent was obtained from the parents and child at the time of recruitment.

Acoustic startle response

Acoustic startle was measured using a commercial amplifier system (San Diego Instruments SR-HLAB). Auditory startle probes were administered to participants through calibrated headphones while sitting upright with eyes fixed on a small reticle on a blank wall approximately 3 feet away. Measurement sessions began with a 1-minute acclimatization period of white noise prior to initiation of the startle probes. Participants received 12 startle probes, each 50 milliseconds in duration and 103 decibels loudness delivered with a variable (~10-25 seconds) intertrial interval consistent with published guidelines.[4,7] Following guidelines, mean electromyography (EMG) amplitude (in microvolts) of the eye blink

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

component was recorded at 1000 Hz from the orbicularis oculi muscle via two 10 mm Ag/AgCl electrodes filled with conductive gel and placed under the left eye with a ground electrode placed on the center of the forehead.[4,7] All acoustic startle testing occurred in a single private exam room in the sports medicine clinic.

Acoustic startle data were automatically processed using the SR-HLAB software as the system does not allow manual processing of the raw data. In addition to automatic filtering deemed "proprietary" by the amplifier manufacture, the SR-HLAB software, epoched from 50 milliseconds preprobe to 1000 milliseconds postprobe onset, rectified and smoothed (5 sample rolling average) the raw data. The automated program rejected trials with less than 40 mV peak within the response window.

Data and statistical analysis

Participant group (recent concussion, concussion history, healthy control) was the primary independent variable while the primary dependent variable was mean startle magnitude (μV). We used a one-way analysis of variance followed by a Tukey post hoc test to compare mean startle magnitude among the 3 groups. Checks of model assumptions and outliers identified 1 potential outlier, based on studentized residuals, that did not change any of the results, so this observation was included in the analyses. Significance level was set at 0.05, and all analyses were run using Stata statistical software. Deidentified startle data and analysis scripts will be available on Open Science Framework upon manuscript publication.

RESULTS

Sample size was determined based on power analysis and past literature (see Transparency, Rigor, and Reproducibility Summary). Forty-nine adolescents participated in the study. There were 20 participants in the recent concussion group, 16 in the concussion history group, and 13 healthy control participants (Table 1).

We found significant differences in mean startle magnitude ($F(2,46) = 5.49$, $P = .007$)) among the recent concussion (77.56 ± 23.55 μV), concussion history (77.55 ± 27.48 μV), and healthy control groups (151.09 ± 127.35 μV). Mean startle magnitude was significantly suppressed for the recent concussion compared to the healthy control groups ($t = -3.01$, $P = .01$) and for the concussion history compared to the healthy control groups ($t = -2.87$, $P = .02$). There was not a significant difference between the recent concussion and concussion history groups ($t = 0.00$, $P = 1.00$)* (Figure 1).

DISCUSSION

Athletes in both the concussion and concussion history groups presented with a significantly suppressed general startle reactivity compared to healthy controls with no such history. This provides novel preliminary evidence for possible sensorimotor dysfunction in adolescent athletes who have had diagnosed concussions. It is possible that this suppression resulted from damage to the brainstem circuits from the concussive injury, as the primary neural circuit for acoustic startle is a trisynaptic pathway in the pons and spinal cord,[12] and the brainstem sustains some of the greatest shearing forces following a head impact.[13] However, while the startle circuit is well documented, post-concussion brainstem circuit dysfunction is not well understood, and it is beyond the scope of this preliminary study to delineate an exact underlying mechanism of acoustic startle suppression. Future work in this realm should use a multimodal approach to further clarify concussion's role in general startle reactivity deficits by testing additional mechanisms through assessing, for example, the influence of higher order brain structures that project onto the startle circuit.[7]

The general startle reactivity of the concussion history group remained significantly attenuated and was statistically indistinguishable from the concussion group, suggesting there may be lingering physiological dysfunction beyond currently defined clinical recovery. In an exemplary rodent model of concussion, Pang et al, observed a long-lasting suppression of the acoustic startle response following mild traumatic brain injury induced by lateral fluid percussion.[9] However, their rodent study duration only lasted 21 days, so it is unknown how long the suppressed response may have persisted beyond the study endpoint. Conversely, the median time since recent concussion was 493 days (1.35 years) from their most recent concussion. This signals possible post-concussion dysfunction in humans far beyond what has been observed in animal models (eg, ~ 21 days).[9] Attenuated startle reactivity was also observed in military personnel with a lifetime

*We conducted 2 post hoc exploratory analyses to further assess the group differences: (1) To explore possible habitation differences among the groups, we reanalyzed the data in a mixed ANOVA including repeated measures for Time (First vs Second half of trials). This revealed a main effect of Time ($F(1,46) = 4.47$, $P = .040$) as general startle reactivity habituated from the first half (102.5 microvolts) to the second half (91.5 microvolts) across all 3 groups as is commonly seen in for general startle reactivity.[7]. There was no Group by Time interaction ($F(2,46) = 0.22$, $P = .806$) as startle habituation from the first to second half did not appear to vary among the groups. (2) Given the lack of a significant difference between the 2 concussion groups, we pooled the concussion groups and conducted ROC analyses to further explore the potential clinical utility of general startle reactivity to distinguish between individuals with and without any past concussion. This resulted in an AUC of 0.69 (95% CI: 0.48-0.89), suggesting general startle reactivity has near acceptable discriminate validity in this sample. At the optimal threshold of 90.2 (Youden's J index) the model demonstrated a sensitivity of 81% and a specificity of 62%. However, all these exploratory analyses should be interpreted cautiously until replicated in a larger sample.

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 1 *Participant demographics.*

	Recent Concussion (n = 20)	Concussion History (n = 16)	Healthy Controls (n = 13)	Total (n = 49)
Age (years)	14.6 ± 1.6	14.8 ± 2.0	13.3 ± 2.8	14.3 ± 2.2
Sex (% female)	60%	44%	54%	53%
Concussion history (%, range)	20/20 (100%) Range: 1-6	20/20 (100%) Range: 1-4	N/A	–
Days from most recent concussion (M ± SD)	31.4 ± 23.0 Median = 32	650.0 ± 734.3 Median = 493	N/A	–
Symptom Severity (M ± SD)	Total: 20.3 ± 22.3 Somatic: 6.7 ± 7.0 Vestibular: 2.8 ± 4.4 Emotional: 2.5 ± 3.4 Cognitive: 6.4 ± 7.9 Sleep: 2.4 ± 3.0	Total: 17.6 ± 13.9 Somatic: 4.3 ± 5.3 Vestibular: 1.5 ± 1.9 Emotional: 3.7 ± 3.4 Cognitive: 4.3 ± 4.9 Sleep: 3.7 ± 2.9	Total: 4.2 ± 5.5 Somatic: 0.92 ± 1.6 Vestibular: 0.3 ± 0.6 Emotional: 1.2 ± 1.8 Cognitive: 1.0 ± 1.9 Sleep: 0.8 ± 1.1	–

Somatic symptoms included headache, pressure in head, neck pain, nausea/vomiting, sensitivity to light, and sensitivity to noise. Vestibular symptoms included balance problems, dizziness, and blurred vision. Emotional symptoms included feeling more emotional, irritability, sadness, and nervous/anxious. Cognitive symptoms included confusion, feeling like in a fog, difficulty concentrating, difficulty remembering, do not feel right, and feeling slowed down. Sleep symptoms included drowsiness, fatigue or low energy, and trouble falling asleep.

history of mild traumatic brain injury.[10] However, the lack of significant differences between the 2 concussion groups in the current study should be interpreted cautiously as our group sizes for this preliminary study were likely underpowered to detect anything but large effects. Likewise, the reported effect sizes we observed for concussion versus non-concussion differences may be an overestimation given our sample size of 49. Future work should use larger samples that allow more power to detect group differences and more precisely estimate such differences.

Lingering and difficult-to-detect post-concussion sensorimotor impairments may contribute to an increased likelihood of subsequent musculoskeletal injury in the year following concussion for some athletes, particularly in the immediate months following return to sport.[2,14] Currently, clinicians are unable to identify who is at higher risk of subsequent musculoskeletal injury following concussion. Deficits uniquely characterized by psychophysiological measures such as general startle reactivity may be associated with subsequent injury and requires empirical study. Existing neuroimaging and biological tests may detect lingering sensorimotor deficits but such methods remain costly, often inaccessible, and invasive.[15] General startle reactivity's relative noninvasiveness and low cost has the potential to address a need for more sensitive and clinically feasible markers of concussion recovery.

General startle reactivity presents as a uniquely promising tool for identifying post-concussion deficits which may inform return-to-sport decisions, but its current application and understanding are not without limitations and challenges. For example, the cross-sectional design of this preliminary work precludes knowledge of each concussion group's general startle reactivity prior to injury. This limits the ability to attribute group differences to concussion rather than preexisting differences. Relatedly, our recent concussion group was approximately 1 month out from their concussion yet still clinically symptomatic, suggesting this cohort may have had slower than normal clinical recovery.[16] Clearer evidence of post-concussion deficiency, in general, startle reactivity and its persistence, will require longitudinal approaches that repeatedly assess acute concussion, long after athletes are cleared to return to sport. Furthermore, studies designed to correlate general startle reactivity with measures of motor function (eg, gait analysis) and clinical outcomes (eg, individual symptoms and symptom severity; neurocognitive performance; subsequent injury) will increase researcher and clinician understanding of this potentially informative marker in adolescents.[17]

CONCLUSIONS

General startle reactivity has been assessed by researchers focused on both non-human animals and humans as a translational measure of brainstem-mediated physiological reactivity for decades.[8] The results presented here suggest that general startle

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

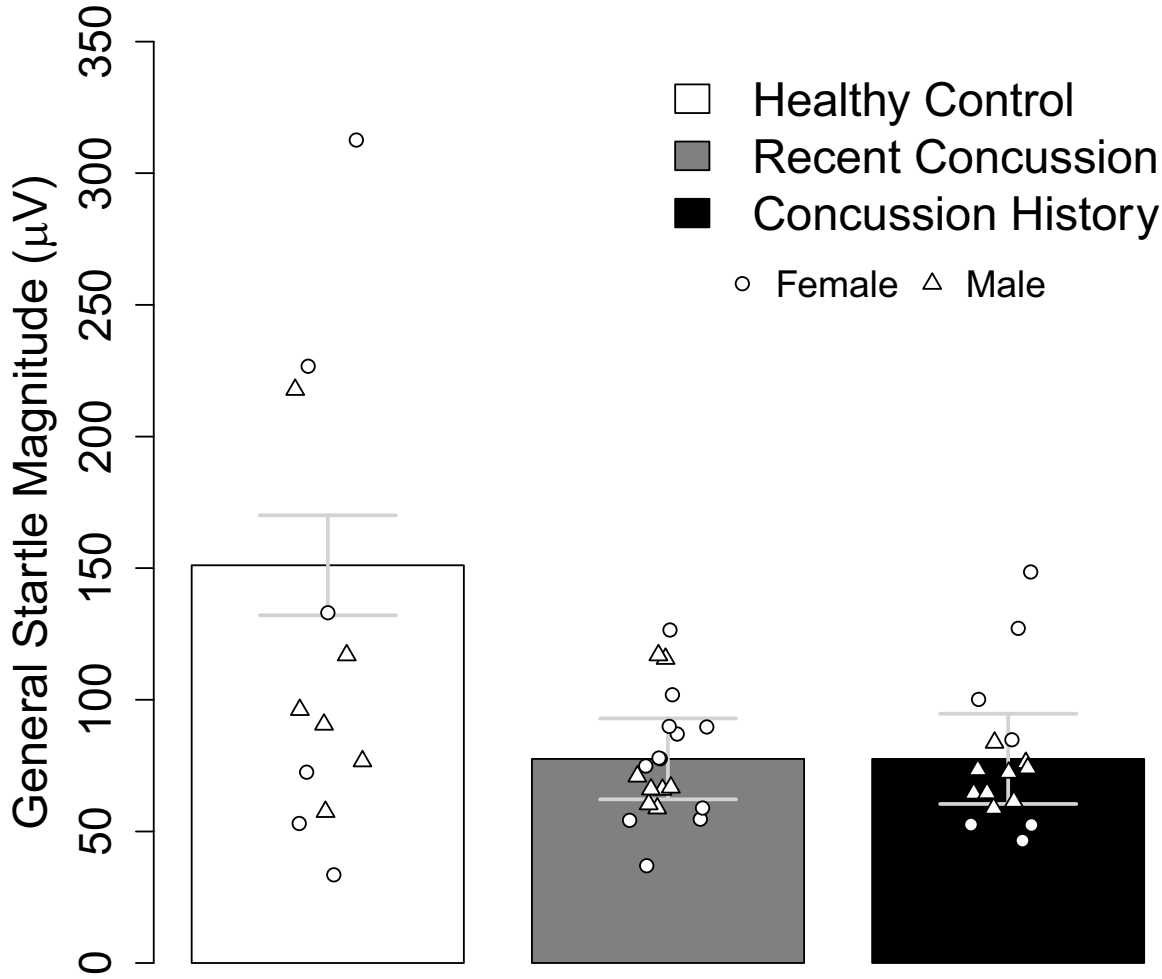

Figure 1. General startle magnitude by group. Error bars represent ±1 standard error of the mean. Points represent raw data within each group.

reactivity is a potential biomarker for concussion. Furthermore, our novel findings may provide additional insight into the mechanisms of concussion and increased incidence of subsequent injuries.

TRANSPARENCY, RIGOR, AND REPRODUCIBILITY SUMMARY

This study was primarily conducted to inform future preregistered studies. The pwr package in R indicated that N = 14 in each group provided at least 80% power using an alpha level of .05 (2 tailed) to detect a d effect size of .98 which is the effect size detected for recent concussion versus healthy control group differences in rodent concussion literature on which this study is based.[9] The study sample size was ultimately determined balancing minimum group sample size from the power analysis and grant funding timeline restrictions. Over a 2-year period, startle data were obtained and successfully analyzed in 49 participants (20 recent concussion, 16 concussion history, 13 healthy controls). Study team members were not blinded to concussion status since startle (the primary DV) is not under volitional control. Startle was measured using a proprietary system (San Diego Instruments SR-HLAB) in accordance to published guidelines.[7] The key inclusion criteria and outcome evaluations are established standards. Large replication studies are currently in progress. Upon publication of the manuscript, deidentified data and analytic code from this study will be publicly available at on open science framework (OSF). All data used to conduct the study were obtained by the investigators, and all participants have provided permission data to be used for future research without requirement for specific additional informed consent. A preprint of this paper will be published under a Creative Commons Open Access license, and upon publication will be freely available and linked from the OSF study repository.

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

REFERENCES

1. Veliz P, McCabe S, Eckner J, et al. Prevalence of concussion among US adolescents and correlated factors. JAMA. 2017;318 (12):1180–1182. doi:10.1001/jama.2017.9087
2. Smulligan K, Wilson J, Howell D. Increased risk of musculoskeletal injuries after concussion. *Oper Tech Sports Med*. 2022;30 (1):1–11. doi:10.1016/j.otsm.2022.150896
3. Kamins J, Bigler E, Covassin T, et al. What is the physiological time to recovery after concussion? A systematic review. *Br J Sports Med*. 2017;51(12):935–940. doi:10.1136/bjsports-2016-097464
4. Kaye J, Bradford D, Curtin J. Psychometric properties of startle and corrugator response in NPU, affective picture viewing, and resting state tasks. *Psychophysiology*. 2016;53(8):1241–1255. doi:10.1111/psyp.12663
5. Hirad A, Bazarian J, Merchant-Borna K, et al. A common neural signature of brain injury in concussion and subconcussion. *Sci Adv*. 2019;5(8):1–11. doi:10.1126/sciadv.aau3460
6. Viano D, Casson I, Pellman E, et al. Concussion in professional football: comparison with boxing head impacts–Part 10. *Neurosurgery*. 2005;57(6):1154–1172. doi:10.1227/01.NEU.0000187541.87937.D9
7. Blumenthal T, Cuthbert B, Filion D, et al. Committee report: guidelines for human startle eyeblink electromyographic studies. *Psychophysiology*. 2005;42(1):1–15. doi:10.1111/j.1469-8986.2005.00271.x
8. Grillon C, Baas J. A review of the modulation of the startle reflex by affective states and its application in psychiatry. *Clin Neurophysiol*. 2003;114(9):1557–1579. doi:10.1016/s1388-2457(03)00202-5
9. Pang K, Sinha S, Avcu P, et al. Long-lasting suppression of acoustic startle response after mild traumatic brain injury. *J Neurotrauma*. 2015;32(11):801–810. doi:10.1089/neu.2014.3451
10. Wright WG, Handy JD, Avcu P, et al. Healthy active duty military with lifetime experience of mild traumatic brain injury exhibits subtle deficits in sensory reactivity and sensory integration during static balance. *Mil Med*. 2018;183(suppl_1):313–320. doi:10.1093/milmed/usx182
11. Patricios JS, Schneider KJ, Dvorak J, et al. Consensus statement on concussion in sport: the 6th International Conference on Concussion in Sport–Amsterdam, October 2022. *Br J Sports Med*. 2023;57(11):695–711. doi:10.1136/bjsports-2023-106898
12. Koch M. The neurobiology of startle. *Prog Neurobiol*. 1999;59 (2):107–128. doi:10.1016/s0301-0082(98)00098-7
13. Zhang L, Yang KH, King AI. A proposed injury threshold for mild traumatic brain injury. *J Biomech Eng*. 2004;126(2):226–236. doi:10.1115/1.1691446
14. Oldham J, Howell D, Knight C, et al. Gait performance is associated with subsequent lower extremity injury following concussion. *Med Sci Sports Exerc*. 2020;52(11):2279–2285. doi:10.1249/MSS.0000000000002385
15. Senaratne N, Hunt A, Sotsman E, et al. Biomarkers to aid the return to play decision following sports-related concussion: a systematic review. *J Concussion*. 2022;6:1–7. doi:10.1177/20597002211070735
16. Putukian M, Purcell L, Schneider KJ, et al. Clinical recovery from concussion-return to school and sport: a systematic review and meta-analysis. *Br J Sports Med*. 2023;57(12):798–809. doi:10.1136/bjsports-2022-106682
17. Servatius RJ, Spiegler KM, Handy JD, et al. Neurocognitive and fine motor deficits in asymptomatic adolescents during the subacute period after concussion. *J Neurotrauma*. 2018;35 (8):1008–1014. doi:10.1089/neu.2017.5314

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.