Eye Tracking as a Biomarker for Concussion in Children

Abdullah Bin Zahid, MD,*†‡ Molly E. Hubbard, MD,*† Julia Lockyer, MS,§ Olivia Podolak, MD,§
Vikalpa M. Dammavalam, BS,*†‡ Matthew Grady, MD,§¶ Michael Nance, MD,§ Mitchell Scheiman, OD, PhD,‖
Uzma Samadani, MD, PhD,*†‡ and Christina L. Master, MD§¶

Abstract

Objective: Concussion is the most common type of brain injury in both pediatric and adult populations and can potentially result in persistent postconcussion symptoms. Objective assessment of physiologic "mild" traumatic brain injury in concussion patients remains challenging. This study evaluates an automated eye-tracking algorithm as a biomarker for concussion as defined by its symptoms and the clinical signs of convergence insufficiency and accommodation dysfunction in a pediatric population. **Design:** Cross-sectional case–control study. **Setting:** Primary care. **Patients:** Concussed children (N = 56; mean age = 13 years), evaluated at a mean of 22-week post-injury, compared with 83 uninjured controls. **Independent Variables:** Metrics comparing velocity and conjugacy of eye movements over time were obtained and were compared with the correlation between Acute Concussion Evaluation (ACE) scores, convergence, and accommodation dysfunction. **Main Outcome Measures:** Subjects' eye movements recorded with an automated eye tracker while they watched a 220-second cartoon film clip played continuously while moving within an aperture. **Results:** Twelve eye-tracking metrics were significantly different between concussed and nonconcussed children. A model to classify concussion as diagnosed by its symptoms assessed using the ACE achieved an area under the curve (AUC) = 0.854 (71.9% sensitivity, 84.4% specificity, a cross-validated AUC = 0.789). An eye-tracking model built to identify near point of convergence (NPC) disability achieved 95.8% specificity and 57.1% sensitivity for an AUC = 0.810. Reduced binocular amplitude of accommodation had a Spearman correlation of 0.752(*P* value <0.001) with NPC. **Conclusion:** Eye tracking correlated with concussion symptoms and detected convergence and accommodative abnormalities associated with concussion in the pediatric population. It demonstrates utility as a rapid, objective, noninvasive aid in the diagnosis of concussion.
Key Words: accommodation, brain injury, concussion, convergence, eye tracking

(*Clin J Sport Med* 2018;00:1–11)

INTRODUCTION

Concussion is the result of a biomechanical force to the head that disrupts the normal function of the brain.[1] Although this definition seems unambiguous, the quantification of brain function is challenging, which is why the diagnosis of concussion still remains subjective. This problem is frequently solved in adult sports setting by requiring athletes to undergo pre-injury testing. However, children may be suboptimal candidates for concussion diagnostics that rely on pre-injury assessment of volitional tasks subject to developmentally evolving capabilities, such as reading, writing, and speaking.[2] Similarly, subjects presenting to the emergency department (ED) after a suspected blow to the head without pre-injury testing also pose a challenge to the diagnosis of concussion. The CDC reports 335 966 emergency visits for traumatic brain injury (TBI) by children aged 5 to 14 years in 2013, of which about 75% (252 565) were from unintentional falls and/or unintentionally stuck by another object.[3,4] It is unlikely that these children had any pre-injury testing. Thus, objective assessment of physiologic brain injury in children is an important goal in the field.

Currently, for the purposes of clinical diagnosis, despite its limitations, CDC has adapted[5] the Acute Concussion Evaluation (ACE) symptom checklist[6] developed by Lovell and Collins.[7] It has been validated in the pediatric population and is frequently used as a starting point to develop objective tests for concussion.[8] Several variations of this list of 22 symptoms are currently recommended in place of previously established concussion grading scales that primarily rely on assessing loss of consciousness (LOC), confusion, and amnesia.[9–11]

Among objective markers, eye tracking, using an infrared camera to detect and quantify eye movements, has previously

Submitted for publication September 27, 2017; accepted May 30, 2018.

*From the *Department of Surgery, Hennepin County Medical Center, Minneapolis, Minnesota; †Department of Neurosurgery, University of Minnesota, Minneapolis, Minnesota; ‡Surgical Services, Minneapolis VA Health Care System, Minneapolis, Minnesota; §Sports Medicine and Performance Center, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; ¶Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and ‖Pennsylvania College of Optometry at Salus University, Pennsylvania.*

Supported by departmental funding to the principal investigators (U.S. and C.L.M.) at their respective institutions.

A.B. Zahid and U. Samadani have submitted intellectual property related to the technology used in this article. These patents are owned by New York University (NYU), the Department of Veteran Affairs (VA), and Hennepin County Medical Center (HCMC) and licensed to Oculogica Inc, a company in which U. Samadani, NYU, the VA, and HCMC all have an equity interest. U. Samadani also has grant funding from and has served as an advisor for Abbott Diagnostic Laboratories. U. Samadani and M.E. Hubbard also have grant funding from Integra Inc. The remaining authors report no conflicts of interest.

Portions of this work were presented in abstract form at a Sports Medicine meeting in June 2016.

Corresponding Author: Uzma Samadani, MD, PhD, 701 Park Ave S PL. 610, Minneapolis, MN 55415 (Uzma.Samadani@hcmed.org).

http://dx.doi.org/10.1097/JSM.0000000000000639

been shown to be effective and efficient in assessing concussion and central nervous system integrity by quantitatively detecting abnormalities in oculomotor neural pathways in the adult population.[12–14] Furthermore, studies have shown that there are additional changes in eye tracking associated with elevations in intracranial pressure in more critically ill patients with severe TBI.[15] The development of algorithms to interpret the abnormalities in eye movement seen after concussion has the potential to be used as a tool to objectively diagnose concussion, even in patients without any pre-injury testing.

The vestibulo-ocular testing and vision assessment is another avenue that allows for objective assessment of concussion. Studies report that 28%[16] to 69%[6] of concussed children have clinical signs of vestibular or oculomotor dysfunction such as blurred or double vision, difficulty in sustaining visual attention, and loss of place when reading.[6] The near point of convergence (NPC) is a clinical test that determines the convergence amplitude by measuring the closest distance to which a subject can maintain single vision, as an object is moved toward the eyes. It is 1 of 3 clinical measures used to reach a diagnosis of convergence insufficiency, which is a common concussion-related vision disorder. Another useful test is amplitude of accommodation that is usually not only performed monocularly but can also be performed binocularly during the NPC task.[17] Recent studies have shown that the NPC result correlates with severity of symptoms in concussed populations and may be used in athlete sideline assessment tools.[6,18] Abnormal NPC measurements occur in about 45% of pediatric athletes after sports-related concussion[19] as opposed to 2% to 8% in the general pediatric population without concussion.[6] This is likely due to the fact that intact vision and vestibulo-ocular reflexes require integrity of numerous areas of the brain (occipital lobe, parietal lobe, frontal eye field, brainstem, as well as tracts connecting them).[20] As concussion likely represents a diffusely distributed injury, vision diagnoses may have a high prevalence in adolescents with concussion.

The aim of this study is to assess the utility of eye tracking to identify concussion in a pediatric population who did not receive pre-injury eye-tracking assessment. A second aim was to study the clinical vision assessments of convergence and accommodation in pediatric settings. We hypothesize that children with concussions and persistent postconcussive symptoms will have abnormal eye tracking when compared to children without history of head injury.

METHODS

This study received IRB approval from both centers involved in this study. Concussed subjects were recruited from a concussion referral center at Children Hospital of Philadelphia, Philadelphia, PA.

Subject Selection

Controls were non–brain-injured persons from the general population, siblings of pediatric patients, and children of employees and volunteers visiting the neurosurgery clinic or hospital. Inclusion criteria for cases were as follows: age less than 22 years [US Food and Drug Administration (FDA) definition of pediatrics],[21] intact ocular motility, vision correctable to within 20/500 bilaterally, ability to provide a complete ophthalmologic, medical, and neurologic history, medications consumed within past 24 hours, and no concussion within past 3 years. Parents were asked to corroborate details of the above for children aged 4 to 17 years.

Subjects were excluded if they were noted to have a history of strabismus, diplopia, palsy of cranial nerve (CN) III, IV, or VI, papilledema, optic neuropathy or other known disorder of CN II, macular edema, retinal degeneration, dementia or cognitive impairment, sarcoidosis, myasthenia gravis, and multiple sclerosis or other demyelinating disease. Comatose and sedated individuals were excluded. Pregnant individuals, prisoners, and subjects who were missing eyes, not opening eyes, or wearing excessive mascara/false eyelashes were excluded from the study.

All patients were recruited from a concussion referral center and were subjected to the same inclusion and exclusion criteria as controls except for recent head injury.

Definition of Concussion and Postconcussion

Concussion was defined according to the Consensus Statement on Concussion in Sports: 4th International Conference on Concussion in Sport Held in Zurich, November 2012.[1] The clinical diagnosis of concussion was made by an experienced clinician according to the aforementioned definition. Acute Concussion Evaluation symptom checklist[5] was used as an adjunct to the clinical diagnosis. This checklist suggests follow-up with the clinician if there is a positive injury description with evidence of forcible direct/indirect blow to the head, evidence of trauma-related active symptoms of any type and number (total symptom score >0), with or without evidence of LOC, skull fracture, or intracranial injury. Postconcussion was defined as persistence of any of the above symptoms after 28 days of having concussion.[22,23]

Eye-Tracking Procedure

Subjects' eye movements were recorded with an SR Research Eyelink 1000 eye tracker while a 220-second video was played continuously within a square aperture moving around the perimeter of a 17″ viewing monitor (aspect ratio 4:3) fixed 55 cm away from the patient. The video aperture size was approximately 1/9th the area of the display monitor. The positions of the eyes were obtained at 500 Hz with a stabilized chin rest to minimize head movement during the eye-tracking session. All subjects were asked to take off their glasses when being tracked. The visual stimuli were Disney music videos (eg, Lion King, Hercules, and Puss in Boots). The total visible span of the moving aperture was approximately 17° horizontally and 13° vertically from midposition with a caveat that the subject may be viewing different portions of the aperture during each cycle. The first and last 10 seconds of each data set were discarded to yield 200 seconds of data, resulting in 100 000 data points. Both the afferent stimulus presentation and eye tracking were binocular. Subjects were not spatially calibrated to the tracker to enable independent analysis of each pupil position over time. The eye-tracking data were processed to yield 89 eye-tracking metrics, as discussed previously.[12–14] The eye tracking was performed without operator intervention. Both cases and controls were tracked using the same procedure.

TABLE 1. Demographics of Testing and Training Data Sets in Our Study

Parameter	Data Set				
	Train		Test		Combined
	Control	Case	Control	Case	
Sample size (N)	32	32	51	24	139
Sex					
Female	15	15	34	13	77
Male	17	17	17	11	62
Age (yr)					
Mean	13.41	13.44	18.29	14.71	15.43
Median	13.50	13.50	20.00	15.00	16.00
SD	4.798	4.731	4.383	1.429	4.743
Minimum	4	4	4	12	4
Maximum	21	21	21	17	21

The data were analyzed using a computerized algorithm, without any human intervention.

Assessment of Convergence and Accommodation

The assessment of convergence and accommodation is a standard component of ophthalmic physical examination. Although they are important in the evaluation of blurred vision, here we assess them after concussion. For the NPC, the point at which the patient saw double was recorded in centimeters. The double vision measurement represents the NPC. We used a 20/30 column of print and the accommodation rule (Gulden Ophthalmics, Elkins Park, PA) for all measurements. Amplitude of accommodation is a measure of the ability of a patient to accommodate or focus, as an object is slowly moved toward the eyes. Although this technique is traditionally performed monocularly,[17] it can be assessed binocularly during the NPC procedure. We assessed the amplitude of accommodation both monocularly and binocularly. Both tests (NPC and amplitude of accommodation) were performed on all patients by one of the senior investigators (C.L.M.).

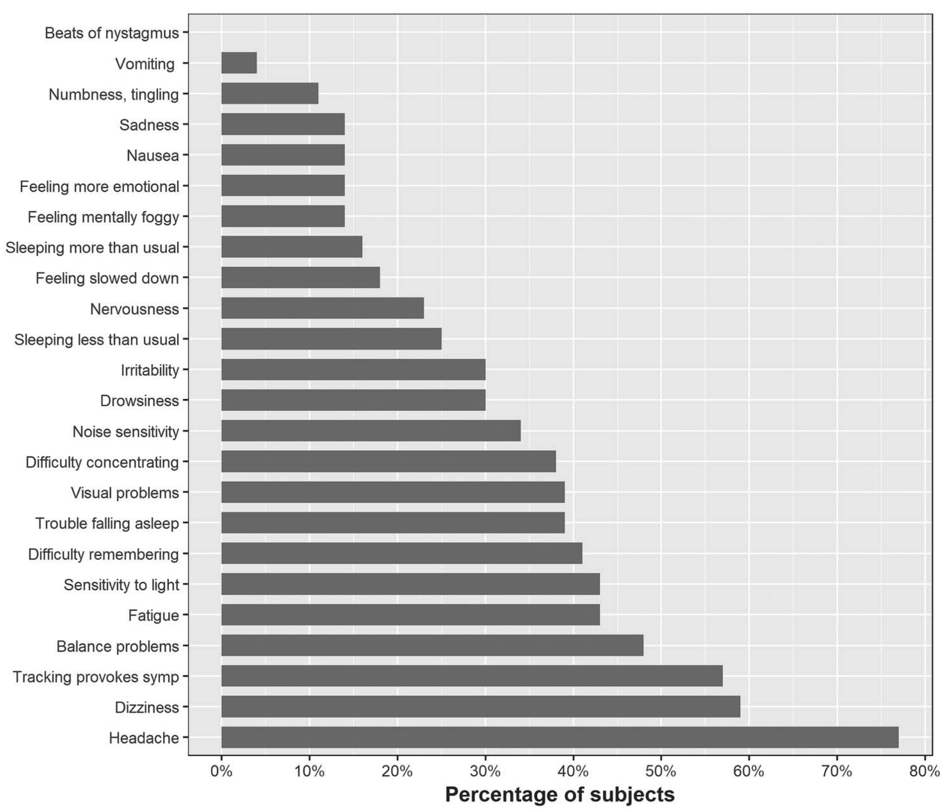

Figure 1. Prevalence of different symptoms in concussed patients.

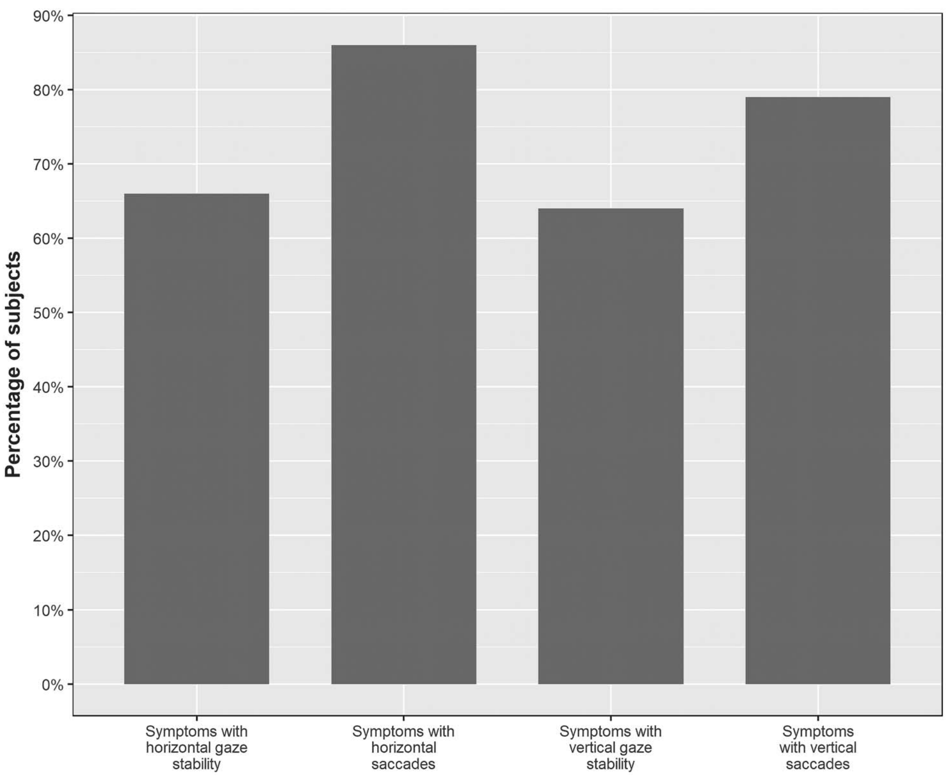

Figure 2. Prevalence of different signs in patients with concussion.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS version 19; IBM Corporation, Armonk, NY) and R programming language, version 3.4.2 from The R Foundation (https://www.r-project.org/). The full statistical analysis is described below in subsections to enhance readability.

Selection of Candidate Eye-Tracking Metrics

The basic approach to analysis was to perform machine learning using logistic regression to predict persistent post-concussion symptoms based on eye tracking. Because there were 89 eye-tracking metrics available to learn from (reported previously[12–14]), feature selection was performed by identifying the metrics whose medians were different between the concussed versus healthy controls using the Wilcoxon rank-sum (also known as the Mann–Whitney *U*) test. In the second step, among the metrics identified previously, the ones associated with sex and age were dropped because an ideal biomarker should be independent of them. This association was determined using Wilcoxon rank-sum tests (for sex vs eye-tracking metrics, with P value <0.05) and Spearman correlation (for age vs eye-tracking metrics, with Spearman correlation >0.35). Finally, in the third step, the remaining metrics were examined for multicollinearity between them,

TABLE 2. ***P* Values and Spearman Correlation for Each Candidate Eye-Tracking Metric As It Relates to Concussion Versus Control, Male Versus Female, and Age**

Parameters	*P* (2-Tailed); Case vs Control	*P* (2-Tailed); Male vs Female	Spearman Correlation for Age
left_distBot_value	<0.001	0.212	−0.112
left_distLef_value	<0.001	0.56	−0.112
right_distBot_value	<0.001	0.17	−0.165
right_distRit_value	<0.001	0.31	−0.183
conj_varXtopbotRatio_value	0.001	0.073	0.125
right_skewRit_value	0.003	0.649	−0.205
right_skewRitNorm_value	0.004	0.733	−0.2
conj_varXbot_value	0.012	0.101	−0.135
left_skewRit_value	0.013	0.857	−0.153
left_skewRitNorm_value	0.024	0.857	−0.13
left_varYtop_value	0.024	0.427	−0.007
conj_varYtopbotRatio_value	0.025	0.023	−0.039

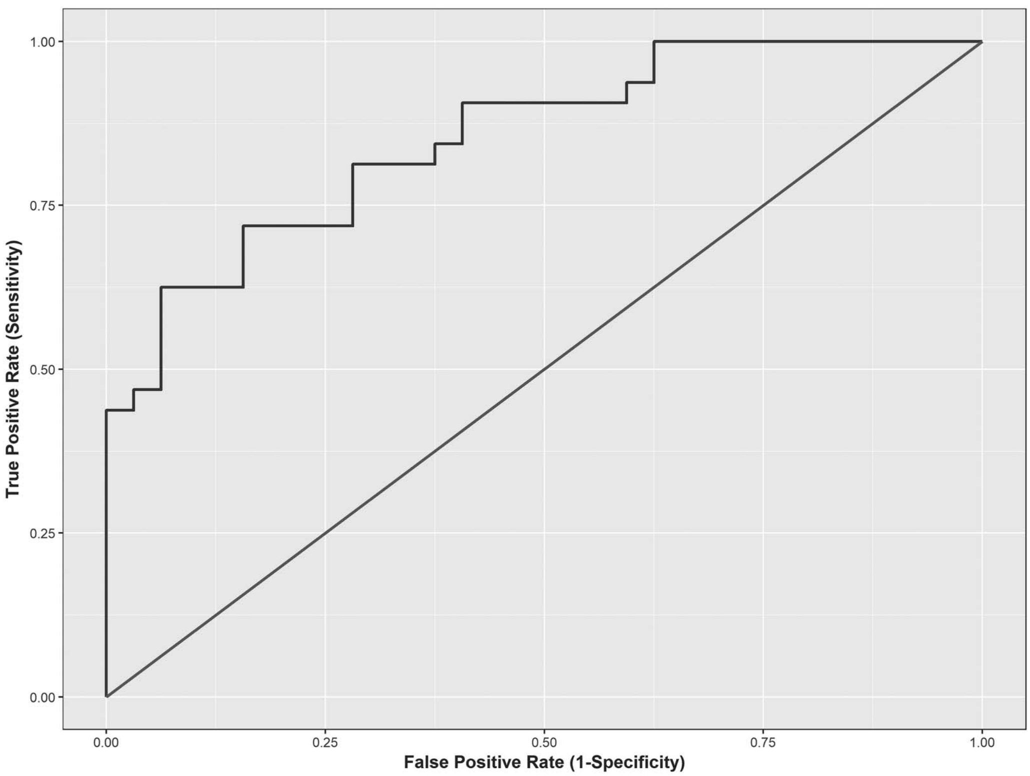

Figure 3. Receiver operating curve for eye tracking as a method of diagnosing concussion in the balanced sample of 32 patients and 32 control subjects. The AUC was 0.854.

and the measures with high correlation with the remainder were excluded. The metrics thus selected after the third step were used to build the model.

Development and Validation of a Predictive Biomarker for Concussion and Postconcussion

About 70% of our concussed subjects were 12 to 17 years, whereas 57% of our controls were 19 to 21 years of age. Although the metrics having high association with age and sex were dropped previously, there was a concern that a randomly divided data set into training and test data sets would result in the model learning age difference even with metrics not overtly associated with it. Hence, to develop a predictive model for concussion, an age and sex-balanced sample was drawn by matching each individual in the cases with a same sex control of age ±1 year as a training data set. The remaining cases were used as a test data set.

The metrics selected in the feature selection step were entered into logistic regression, and a predictive model was built using the stepwise forward method correlating eye-tracking metrics with the presence or absence of persistent postconcussion symptoms. Any metric that significantly added to the existing model ($P < 0.05$) was included in the next step, and those who lost significance ($P > 0.10$) were removed. Every effort was made to arrive at a parsimonious model without sacrificing predictive power. A receiver operating curve (ROC) analysis was conducted for this model (on the training data set), and an optimal cutoff was determined using Youden's index (ie, the point that maximized the sum of sensitivity and specificity). The frequencies of true positive, true negative, false positive, and false negative were calculated to appraise the model accuracy. The resulting model was externally validated in the test data set not used in building the model using ROC analysis and contingency table.

Development and Validation of a Predictive Biomarker for Convergence Insufficiency

In addition to serving as a diagnostic tool for visual cause of persistent postconcussion symptoms, correlation of eye tracking with abnormal NPC was also tested. Candidate eye-tracking metrics that significantly correlated with NPC abnormalities (NPC >6 cm) were identified using the Wilcoxon rank-sum tests. The parameters thus identified were used to build a model to predict the probability of having an abnormal NPC. A ROC analysis was conducted to appraise model accuracy.

Prediction of Individual Symptoms With Eye Tracking

We also tested which symptoms in this population could best be predicted by individual eye-tracking metrics. We created decision trees (with a maximum depth of 3) to predict each symptom and then calculated the balanced accuracy (BA)[24] to appraise model performance. The entire data set (N = 139) was used for this analysis. We did not balance the data set or split it into test and training data sets because some of the symptoms were present in only very few individuals, rendering that approach nonfeasible. Decision tree analysis was used because it is resilient to nonparametric data such as eye tracking. Balanced accuracy was calculated in this situation to provide a better estimate of model performance in cases where one class is overrepresented.[24]

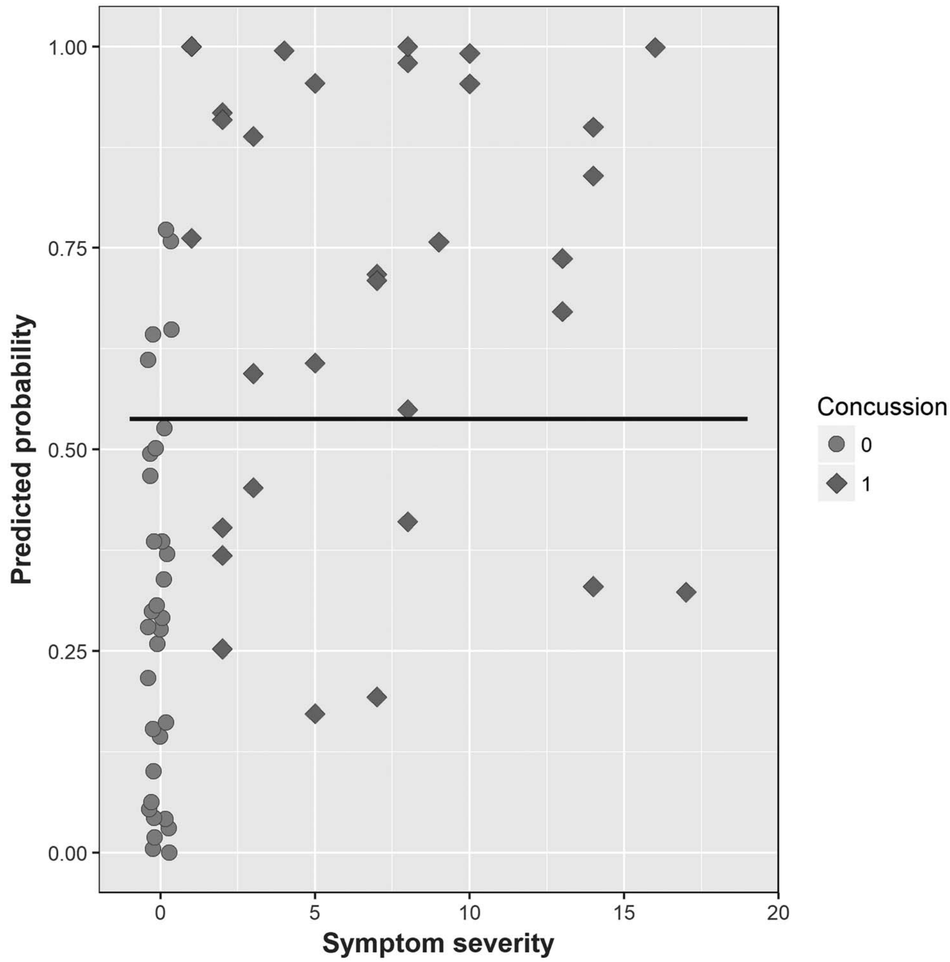

Figure 4. Scatter plot showing the predicted probability of concussion for cases and controls in the balanced sample. Concussed patients are identified by rhombuses, whereas controls are identified by circles. The solid line indicates the model cutoff, above which model will classify subject as concussed.

RESULTS

A total of 56 concussed pediatric patients and 83 non-concussed pediatric controls underwent eye tracking prospectively. Table 1 shows the demographics of cohort who participated in this study. Fifty percent of the concussed patients presented with a sports-related mechanism of injury including being struck by an object or person, fall, and unknown. Other non–sports-related mechanisms included motor vehicle crash and assault. The patients were an average of 22.4 weeks (range: 0-109 weeks) post-injury. Most patients were referred to the concussion center after being diagnosed by another health care provider with a concussion.

In concussed patients, the symptom score was ranked on a scale from 1 to 22 as described in the ACE checklist. The data ranged from 1 to 17 indicating that the highest score was never reached in this population. Figure 1 displays the prevalence of different symptoms in the concussed population. Consistent with previously reported literature on most common symptoms after concussion, headache was present in 76.8% of patients and dizziness in 58.7%. Figure 2 displays the prevalence of different signs in concussed patients. Of the concussed group, clinical testing by horizontal saccades elicited symptoms in 85.7% cases, whereas with vertical saccades, 78.6% of the patients became symptomatic.

To balance age and sex in both groups, a subset comprising 32 cases (age, mean ± SD = 13.43 ± 4.73 years; 15 females) and 32 controls (age, mean ± SD = 13.40 ± 4.79 years; 15 females) was extracted. Groups in the balanced sample did not differ by age (*P* value = 0.979). Of 89 eye-tracking metrics, 12 significantly correlated with concussion (*P* value <0.05) are listed in Table 2. Their correlation with sex (*P* values) and age (Spearman's rho) are also reported. These metrics were examined for multicollinearity, and 4 metrics were excluded because of their high correlation with remaining metrics.

A logistic regression model that correlated eye-tracking metrics with the state of having a concussion was subsequently built. The final model contained 4 metrics (left_distLef—distance traveled by the left eye while watching the video on left, right_distRit—distance traveled by the right eye while watching the video on right, conj_varXtopbotRatio—ratio of the horizontal variance of both eyes while watching video on the top vs bottom, and left_varYtop—vertical variance of the left eye while watching video on the top), all contributing significantly to the model (*P* values <0.05). An ROC curve analysis was performed to compare the probability of having a concussion as predicted by our model to the state of being concussed. On the training data set, the area under the curve (AUC) in the ROC (Figure 3) was 0.854 with a 95% confidence interval of 0.764 to 0.943. The cutoff point

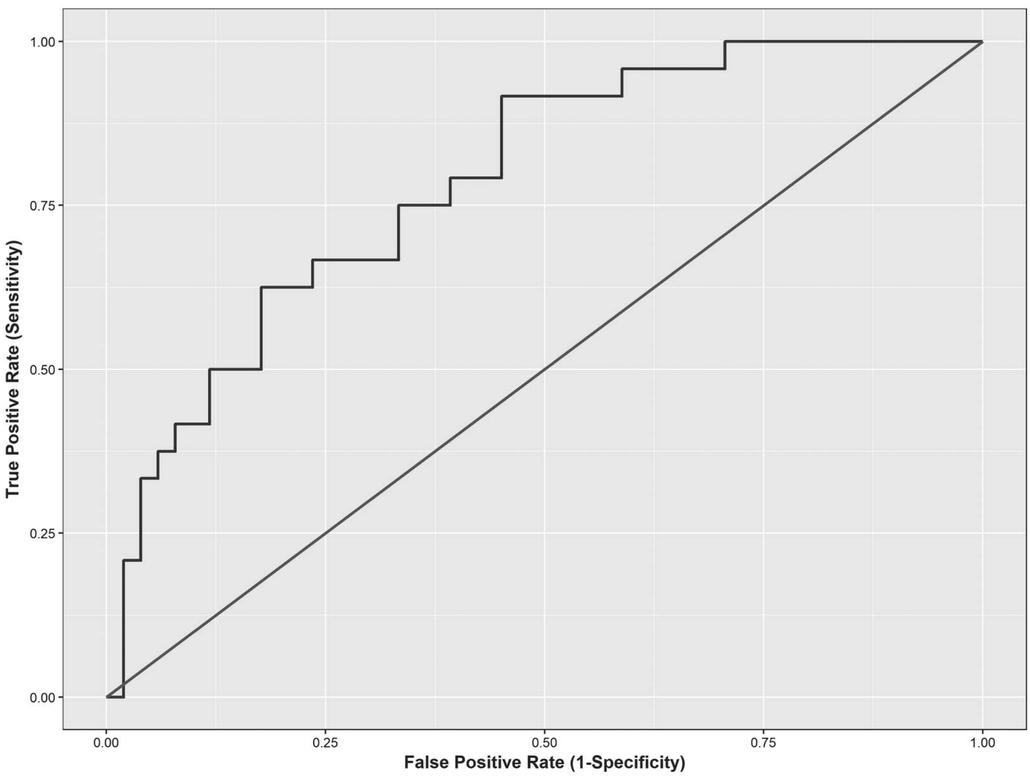

Figure 5. Receiver operating curve for eye tracking as a method of diagnosing concussion in a cross-validation sample of 24 patients and 51 control subjects. The AUC was 0.789.

selected by the maximum of the Youden's Index (maximum of sensitivity + specificity), yielded a model with 78.1% accuracy, 71.9% sensitivity, and 84.4% specificity. The distribution of true and false positives and negatives as a function of predicted probability and symptom score in this validation data set is graphically articulated in Figure 4.

The model was validated in a population of 24 patients and 51 controls. The AUC was 0.789 in this external population (Figure 5). At a predetermined threshold, the sensitivity was 75.0% and specificity was 64.7%. The age range and sex of subjects in the cross-validation data set was the same as the balanced data set used for model building (4-21 years from both sexes). The distribution of true and false positives and negatives as a function of predicted probability and symptom severity in this validation data set can be seen in the scatter plot below (Figure 6). Compared to Figure 4, more controls were falsely labeled as having a concussion in this cross-validation data set, probably secondary to the fact that the cross-validation data set had more subjects with ages greater than 20 years.

Adult Versus Pediatric Eye-Tracking Metrics

Eye-tracking metrics of this pediatric concussion center referral population were compared with our previously published eye-tracking metrics in an adult ED population. Six metrics (conj_varXbot—horizontal variance of both eyes while watching the video at the bottom of the screen, left_distBot—cumulative distance traveled by the left eye while watching video at the bottom, left_distLef—cumulative distance traveled by the left eye while watching video on the left, left_varYtop—vertical variance of the left eye while watching video on the top, right_distBot—cumulative distance of the right eye while watching video on the bottom, and right_distRit—cumulative distance of the right eye while watching video on the right) were found to be significant for both adult and pediatric populations. This overlap indicates that some eye-tracking metrics related to concussion are strongly conserved in adult ED and pediatric concussion referral center populations. However, 6 other metrics (right_skewRitNorm—normalized skewness of the right eye while watching video on the right side, left_skewRit—skewness of the left eye while watching video on the right side, right_skewRit—skewness of the right eye while watching video on the right side, left_skewRitNorm—normalized skewness of the left eye while watching video on the right side, conj_varXtopbotRatio—ratio of the horizontal variance of both eyes while watching video on the top vs bottom, and conj_varYtopbotRatio—ratio of the vertical variance of both eyes while watching video on the top vs bottom) were found significant in children but not in adults.

Amplitude of Accommodation

Table 3 displays the NPC, left and right monocular amplitude of accommodation (MAA), and binocular amplitude of accommodation (BAA) range in 32 concussed subjects used in model building. Because NPC reaches a natural limit very close to its normal value, it was found to be relatively positively skewed (skewness: 1.10 kurtosis: 2.03). By contrast, the BAA displayed a distribution that was fairly close to normal (skewness: 0.10 kurtosis: −0.58). The BAA, right MAA, left MAA, and NPC were not correlated with age (Spearman correlations −0.029, 0.182, 0.118, and 0.343, respectively; *P* values >0.05). The

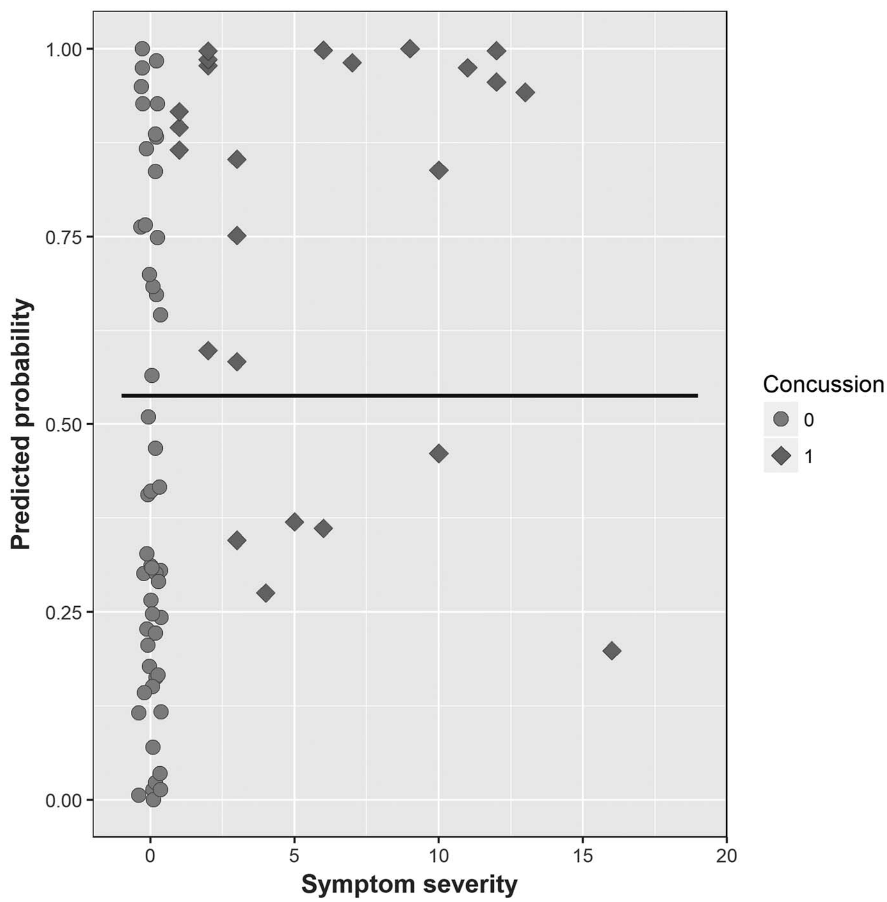

Figure 6. Scatter plot showing the predicted values for cases and controls in the cross-validation sample. Concussed patients are identified by rhombuses, whereas controls are identified by circles. The solid line indicates the model cutoff, above which model will classify subject as concussed.

BAA displayed a moderately strong Spearman correlation of 0.752 (*P* value <0.001) with NPC. Monocular amplitude of accommodation for both right and left eyes, BAA and NPC had higher values in females versus males (Table 4), but none of these values reached significance presumably because of smaller sample size (Table 5). The left and right MAA were strongly correlated with BAA (Spearman correlations: 0.701 and 0.638; *P* values: <0.001 and <0.001, respectively). Near point of convergence was also strongly correlated with BAA (Spearman correlation: 0.615, *P* value <0.001).

Correlation of Eye Tracking With Near Point of Convergence

The correlation between eye-tracking metrics and NPC was tested, and right_velBot (velocity of the right eye while watching video at the bottom) and conj_velRit (velocity of both eyes while watching video on the right) were found to be significant predictors of receded NPC. The model built using these parameters to classify patients based on their NPC status achieved a specificity of 95.8% and a sensitivity of 57.1%. An ROC analysis indicated an AUC of 0.810 (Figure 7).

Correlation of Eye Tracking With Binocular Amplitude of Accommodation

A correlation between eye-tracking metrics and BAA was tested. The following 7 eye-tracking metrics were found to have a strong correlation (R = 0.781) with the BAA: left_velLef—velocity of the left eye while watching video on the left, conj_varX—horizontal variance of both the eyes,

TABLE 3. Performance of the Subjects With Concussion on BAA, MAA, and NPC

Parameters	BAA (cm)	NPC (cm)	Monocular Right Amplitude of Accommodation (cm)	Monocular Left Amplitude of Accommodation (cm)
Mean	7.266	4.919	7.719	8.813
Median	7.000	4.000	7.000	7.750
SD	2.8960	2.8434	4.4376	6.8695
Percentiles				
25	5.250	3.000	5.000	5.000
75	9.000	6.000	9.000	11.125

TABLE 4. Comparisons Between Males and Females in BAA, MAA, and NPC

Parameter	Sex	Mean	SD
BAA (cm)	F	8.133	2.6690
	M	6.500	2.9475
NPC (cm)	F	5.600	2.5579
	M	4.281	3.0275
Monocular right amplitude of accommodation (cm)	F	8.200	2.8082
	M	7.294	5.5539
Monocular left amplitude of accommodation (cm)	F	8.967	3.5126
	M	8.676	8.9773

left_distRit—cumulative distance of the left eye while watching video on the right, right_areamedian—median area of the "boxes" made by the right eye, conj_varYtopbotRatio—ratio of the vertical variance of both eyes while watching video on the top to the bottom, left_heightmean—mean height of the "boxes" made by the left eye, and right_distLef—cumulative distance of the right eye while watching video on the left.

Prediction of Individual Symptoms With Eye Tracking

The symptoms that could be predicted with the most accuracy using eye tracking were (1) nausea (BA of 0.80) with right_widthmean—mean width of the box of the right eye, (2) sensitivity to light (BA = 0.74) with left_varTotal—total variance in the movement of the left eye, (3) feeling mentally foggy (BA = 0.73) with left_skewrit—skewness of the distance of the left eye while looking to the right side, (4) drowsiness (BA = 0.73) with left_aspectratiomean—mean aspect ratio of the box of the left eye, (5) fatigue (BA = 0.73) with left_distlef—cumulative distance traveled by the left eye while watching video on the left side of the box, and (6) sadness (BA = 0.73) with right_velTop—velocity of the right eye while looking up.

DISCUSSION

Concussion is common in the pediatric population,[25] with children most commonly suffering brain injury as the result of an accident, fall, or sports-related activity. However, diagnosing concussion in this population can be difficult because childhood is a critical period of active learning during which the brain undergoes the rapid and ongoing development[26–28]; high levels of plasticity and other developmental differences that characterize immature neural tissue can confound the results of traditional tests for concussion based on pre-injury comparisons.[29,30] Consequently, the development of an objective, noninvasive, and rapid test for concussion that does not rely on pre-injury values is needed to more accurately diagnose pediatric brain injury. Eye-tracking methodologies that assess coordination of movements between the eyes have the advantage of reflecting nonvolitional physiologic brain activity and are a potential alternative to traditional assessments.

Unlike our previous studies of eye tracking that focused on adults recruited through the ED who had been injured a few hours or days previously,[12,13] the pediatric population in this study was recruited from a concussion center a mean of 22-week post-injury following persistent concussive symptoms.[31] Because of this difference, we used an alternative model for predicting concussion in this study. Specifically, we used the binary scored ACE symptom checklist to identify the presence or absence of specific concussion symptoms in the study population. Twelve unique eye-tracking metrics were found to be significantly associated with the presence of concussion in children, several of which were conserved with the acutely injured adult population previously studied. Of note, we found little evidence of a relationship between concussion, as predicted by the model, and the total number of symptoms endorsed, suggesting that detection of concussion using eye tracking is independent of the number of symptoms endorsed. In Figures 4 and 6, the controls are plotted at the very left, consistent with an expectation of no reported concussion symptoms in this group; by contrast, concussed subjects reported anywhere between 1 and 17 symptoms. The ACE, like other common tools, used to aid in the diagnosis of concussion rely on subjectively reported symptoms and is therefore vulnerable to conscious and subconscious variability in reporting. Athletes, for example, may underreport their symptoms for fear of being pulled from a game. Younger children may also report concussion symptoms differently from those in older cohorts.[32] The objective nature of eye tracking coupled with evidence suggesting that eye tracking is not related to the number of symptoms reported provides additional information in the assessment of concussion that is independent of symptoms.

TABLE 5. Comparison of Males and Females for BAA, MAA, and NPC by the *t* Test

			95% Confidence Interval of the Difference	
Parameter	Sig. (2-Tailed)	Mean Difference	Lower	Upper
BAA (cm)	0.113	1.6333	−0.4075	3.6742
NPC (cm)	0.202	1.3187	−0.7472	3.3847
Monocular right amplitude of accommodation (cm)	0.573	0.9059	−2.3401	4.1519
Monocular left amplitude of accommodation (cm)	0.907	0.2902	−4.7606	5.3410

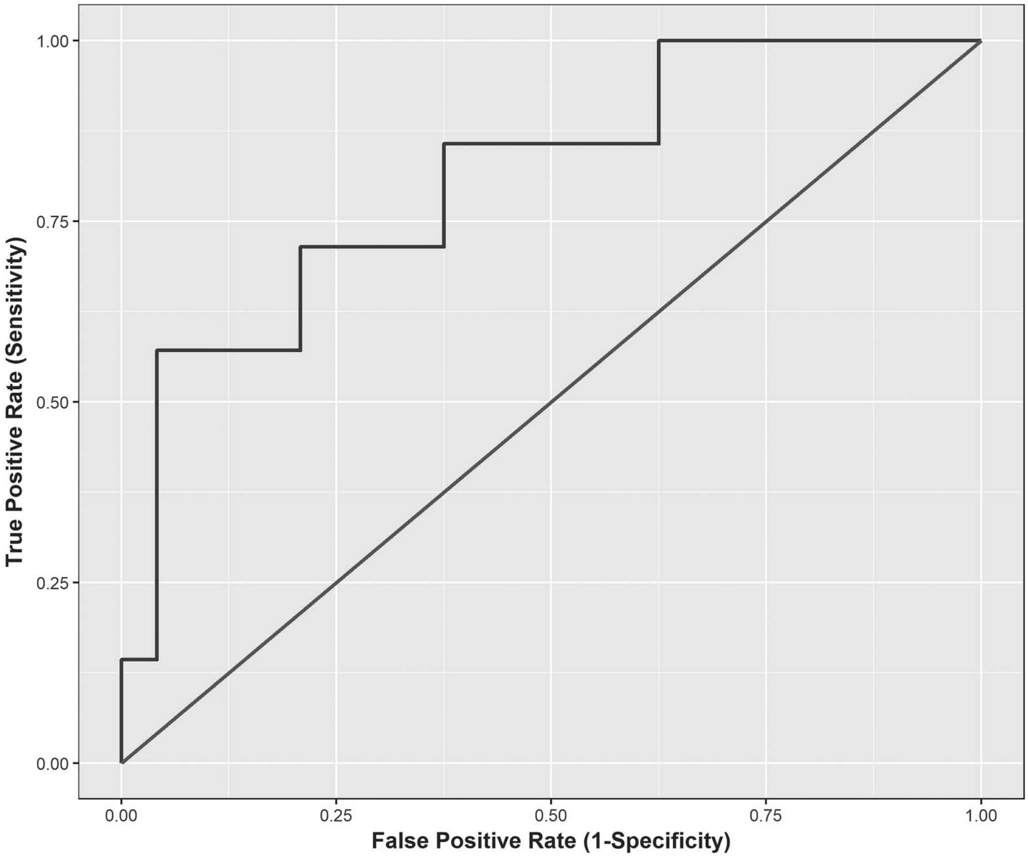

Figure 7. Receiver operating cure for eye tracking as it correlates with abnormality in NPC (as defined by NPC >6 cm) in 32 concussed subjects. The AUC was 0.81.

While eye tracking, as performed in this study, assesses smooth pursuit movements, convergence and accommodation represent a closely related but distinct domain. In this study, we performed NPC, MAA, and BAA. Although accommodative amplitude testing is often performed monocularly,[17] we performed this test both monocularly and binocularly. Both left and right MAA and NPC were strongly correlated with BAA (*P* values <0.001), consistent with previous research indicating that that the BAA might be an additional useful clinical measure for identifying injury associated with concussion.[33] The vision and vestibulo-ocular dysfunction testing can be easily performed at the sidelines to assess concussion during sports. It requires minimal amount of equipment (an accommodation rule) and can be easily performed by the sports team physician or advanced care provider in under 5 minutes. It is cheap, nonproprietary, and can identify objective signs in cases where players do not want to disclose their symptoms.[17]

In our study, none of the 4 vision diagnoses were associated with sex (*P* values >0.05; Tables 3 and 4). However, concussed males had statistically insignificant lower means than concussed females for all 4 clinical parameters (Table 4). These trends are consistent with a substantial body of research demonstrating that concussions are more frequent and associated with worse outcomes in female athletes.[34–37]

A growing number of studies have demonstrated associations between concussion and eye tracking, eye tracking and vision diagnoses after concussion, indicating that concussion may impair eye movement and the clinical assessment of eye movement correlates with automated assessment tools.[6,38–41] Collectively, these studies suggest that oculomotor biomarkers are promising candidates for objective methods of identifying concussion and monitoring recovery.[42,43] Because high-speed cameras can potentially detect very subtle abnormalities in eye movements that are not clinically apparent yet, automated detection using these cameras has the potential to enable greater sensitivity of an objective test to diagnose oculomotor dysfunction associated with concussion and provides an objective measure to track recovery outcomes.

A few limitations of the work being presented should be noted. Subjects without head injury but with body trauma or other orthopedic injuries were not studied; thus, this study is unable to comment on how head injury will compare with other body injuries on eye tracking. Second, the model-building data set was primarily comprised teens, whereas the control subjects in the cross-validation data set were generally older than 20 years. This latter feature of our study could have led to a higher false-positive rate and a lower sensitivity in the cross-validation data set (*cf.* Figures 4 and 6). Further studies on subjects aged 18 to 26 years would be useful to clarify whether patterns of eye-tracking abnormalities demonstrated after concussion are age dependent.

CONCLUSIONS

Eye tracking reliably detected convergence and accommodative abnormalities as well as other types of oculomotor dysfunction associated with concussion in the pediatric population. These results demonstrate the utility of eye tracking as a rapid, objective, noninvasive aid in the diagnosis of concussion that does not require pre-injury data for interpretation.

References

1. McCrory P, Meeuwisse WH, Aubry M, et al. Consensus statement on concussion in sport: the 4th International Conference on concussion in sport held in Zurich, November 2012. *Br J Sports Med*. 2013;47: 250–258.
2. Karlin AM. Concussion in the pediatric and adolescent population: "different population, different concerns". *PM R*. 2011;3(10 suppl 2): S369–S379.
3. Centers for Disease Control. Traumatic brain injury in the United States: fact sheet. 2016. Available at: https://wwwcdcgov/traumaticbraininjury/get_the_factshtml. Accessed May 2017.
4. Taylor CA, Bell J, Breiding M, et al. Traumatic brain injury–related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013. *MMWR Surveill Summ*. 2017;66:1–16.
5. Thomas DG, Collins MW, Saladino RA, et al. Identifying neurocognitive deficits in adolescents following concussion. *Acad Emerg Med*. 2011;18: 246–254.
6. Master CL, Scheiman M, Gallaway M, et al. Vision diagnoses are common after concussion in adolescents. *Clin Pediatr (Phila)*. 2016;55:260–7.
7. Lovell MR, Collins MW. Neuropsychological assessment of the college football player. *J Head Trauma Rehabil*. 1998;13:9–26.
8. Gioia GA, Collins M, Isquith PK. Improving identification and diagnosis of mild traumatic brain injury with evidence: psychometric support for the acute concussion evaluation. *J Head Trauma Rehabil*. 2008;23:230–242.
9. Halstead ME, Walter KD; Council on Sports Medicine and Fitness. American Academy of Pediatrics. Clinical report–sport-related concussion in children and adolescents. *Pediatrics*. 2010;126:597–615.
10. Yeates KO, Taylor HG, Rusin J, et al. Longitudinal trajectories of postconcussive symptoms in children with mild traumatic brain injuries and their relationship to acute clinical status. *Pediatrics*. 2009;123: 735–743.
11. Eisenberg MA, Meehan WP III, Mannix R. Duration and course of post-concussive symptoms. *Pediatrics*. 2014;133:999–1006.
12. Samadani U, Li M, Qian M, et al. Sensitivity and specificity of an eye movement tracking-based biomarker for concussion. *Concussion*. 2015; 1:1–14.
13. Samadani U, Ritlop R, Reyes M, et al. Eye tracking detects disconjugate eye movements associated with structural traumatic brain injury and concussion. *J Neurotrauma*. 2015;32:548–556.
14. Samadani U. A new tool for monitoring brain function: eye tracking goes beyond assessing attention to measuring central nervous system physiology. *Neural Regen Res*. 2015;10:1231–1233.
15. Kolecki R, Dammavalam V, Bin Zahid A, et al. Elevated intracranial pressure and reversible eye-tracking changes detected while viewing a film clip. *J Neurosurg*. 2018;128:811–818.
16. Ellis MJ, Cordingley D, Vis S, et al. Vestibulo-ocular dysfunction in pediatric sports-related concussion. *J Neurosurg Pediatr*. 2015;16: 248–255.
17. Scheiman M, Wick B. *Clinical Management of Binocular Vision: Heterophoric, Accommodative, and Eye Movement Disorders*. 4th ed. Philadelphia, PA: Lippincott; 2014.
18. Mucha A, Collins MW, Elbin RJ, et al. A Brief Vestibular/Ocular Motor Screening (VOMS) assessment to evaluate concussions: preliminary findings. *Am J Sports Med*. 2014;42:2479–2486.
19. Pearce KL, Sufrinko A, Lau BC, et al. Near point of convergence after a sport-related concussion: measurement reliability and relationship to neurocognitive impairment and symptoms. *Am J Sports Med*. 2015.
20. Ciuffreda KJ, Kapoor N, Rutner D, et al. Occurrence of oculomotor dysfunctions in acquired brain injury: a retrospective analysis. *Optometry*. 2007;78:155–161.
21. Food and Drug Administration. Pediatric medical devices. 2018; Available at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ucm135104.htm. Accessed February 26, 2018.
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Washington, DC: American Psychiatric Pub; 2013.
23. Barlow KM. Postconcussion syndrome: a review. *J Child Neurol*. 2016; 31:57–67.
24. Brodersen KH, Ong CS, Stephan KE, et al. The balanced accuracy and its posterior distribution. Paper presented at: 20th international conference on Pattern recognition (ICPR), August 23–26, 2010.
25. McKinlay A, Grace RC, Horwood LJ, et al. Prevalence of traumatic brain injury among children, adolescents and young adults: prospective evidence from a birth cohort. *Brain Inj*. 2008;22:175–181.
26. Kirkwood MW, Yeates KO, Wilson PE. Pediatric sport-related concussion: a review of the clinical management of an oft-neglected population. *Pediatrics*. 2006;117:1359–1371.
27. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*. 2011; 134:2197–2221.
28. Daneshvar DH, Riley DO, Nowinski CJ, et al. Long-term consequences: effects on normal development profile after concussion. *Phys Med Rehabil Clin N Am*. 2011;22:683–700, ix.
29. Putukian M. The acute symptoms of sport-related concussion: diagnosis and on-field management. *Clin Sports Med*. 2011;30:49–61, viii.
30. McCrea M, Hammeke T, Olsen G, et al. Unreported concussion in high school football players: implications for prevention. *Clin J Sport Med*. 2004;14:13–17.
31. Barlow KM, Crawford S, Brooks BL, et al. The incidence of postconcussion syndrome remains stable following mild traumatic brain injury in children. *Pediatr Neurol*. 2015;53:491–497.
32. McCrory P, Meeuwisse W, Aubry M, et al. Consensus statement on concussion in sport–the 4th International Conference on concussion in sport held in Zurich, November 2012. *J Sci Med Sport*. 2013;16:178–189.
33. Green W, Ciuffreda KJ, Thiagarajan P, et al. Static and dynamic aspects of accommodation in mild traumatic brain injury: a review. *Optometry*. 2010;81:129–136.
34. Dick RW. Is there a gender difference in concussion incidence and outcomes? *Br J Sports Med*. 2009;43(suppl 1):i46–i50.
35. Berz K, Divine J, Foss KB, et al. Sex-specific differences in the severity of symptoms and recovery rate following sports-related concussion in young athletes. *Phys Sportsmed*. 2013;41:58–63.
36. Marar M, McIlvain NM, Fields SK, et al. Epidemiology of concussions among United States high school athletes in 20 sports. *Am J Sports Med*. 2012;40:747–755.
37. Covassin T, Swanik CB, Sachs ML. Sex differences and the incidence of concussions among collegiate athletes. *J Athl Train*. 2003;38:238–244.
38. Green W, Ciuffreda KJ, Thiagarajan P, et al. Accommodation in mild traumatic brain injury. *J Rehabil Res Dev*. 2010;47:183–199.
39. Ellis MJ, Cordingley DM, Vis S, et al. Clinical predictors of vestibulo-ocular dysfunction in pediatric sports-related concussion. *J Neurosurg Pediatr*. 2017;19:38–45.
40. Pillai C, Gittinger JW Jr. Vision testing in the evaluation of concussion. *Semin Ophthalmol*. 2017;32:144–152.
41. Singman EL. Automating the assessment of visual dysfunction after traumatic brain injury. *Med Instrum*. 2013;1:3.
42. Ciuffreda KJ, Ludlam DP, Thiagarajan P, et al. Proposed objective visual system biomarkers for mild traumatic brain injury. *Mil Med*. 2014;179:1212–1217.
43. Hunt AW, Mah K, Reed N, et al. Oculomotor-based vision assessment in mild traumatic brain injury: a systematic review. *J Head Trauma Rehabil*. 2016;31:252–261.