Fixational eye movements following concussion

Bianca T. Leonard Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Anthony P. Kontos Department of Orthopedic Surgery, University of Pittsburgh, Pittsburgh, PA, USA

Gregory F. Marchetti Department of Physical Therapy, Duquesne University, Pittsburgh, PA, USA

Min Zhang Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Shawn R. Eagle Department of Orthopedic Surgery, University of Pittsburgh, Pittsburgh, PA, USA

Hope M. Reecher Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Ethan S. Bensinger Vision Science Group, University of California, Berkeley, Berkeley, CA, USA

Valerie C. Snyder Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Cyndi L. Holland Department of Orthopedic Surgery, University of Pittsburgh, Pittsburgh, PA, USA

Christy K. Sheehy Department of Neurology, University of California, San Francisco, San Francisco, CA, USA

Ethan A. Rossi Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; Department of Bioengineering, University of Pittsburgh Swanson School of Engineering, Pittsburgh, PA, USA

The purpose of this study was to evaluate fixational eye movements (FEMs) with high spatial and temporal resolution following concussion, where oculomotor symptoms and impairments are common. Concussion diagnosis was determined using current consensus guidelines. A retinal eye-tracking device, the tracking scanning laser ophthalmoscope (TSLO), was used to measure FEMs in adolescents and young adults following a concussion and in an unaffected control population. FEMs were quantified in two fixational paradigms: (1) when fixating on the center, or (2) when fixating on the corner of the TSLO imaging raster. Fixational saccade amplitude in recent concussion patients (≤ 21 days) was significantly greater, on average, in the concussion group (mean = 1.03°; *SD* = 0.36°) compared with the controls (mean = 0.82°; *SD* = 0.31°), when fixating on the center of the imaging raster ($t = 2.87$, $df = 82$, $p = 0.005$). These fixational saccades followed the main sequence and therefore also had greater peak velocity ($t = 2.86$, $df = 82$, $p = 0.006$) and peak acceleration ($t = 2.80$, $df = 82$, $p = 0.006$). These metrics significantly differentiated concussed from controls (AUC = 0.67–0.68, minimum

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***p* = 0.005). No group differences were seen for the drift metrics in either task or for any of the FEMs metrics in the corner-of-raster fixation task. Fixational saccade amplitudes were significantly different in the concussion group, but only when fixating on the center of the raster. This task specificity suggests that task optimization may improve differentiation and warrants further study. FEMs measured in the acute-to-subacute period of concussion recovery may provide a quick (<3 minutes), objective, sensitive, and accurate ocular dysfunction assessment. Future work should assess the impact of age, mechanism of injury, and post-concussion recovery on FEM alterations following concussion.**

Introduction

Concussions are a major public health problem in the United States, and they involve heterogeneous symptoms, as well as cognitive, vestibular, and ocular impairment (Collins et al., 2016; Harmon et al., 2019). Although not every patient experiences ocular dysfunction, research shows that 30% to 60% of patients experience one or more ocular symptoms and/or impairments (Mucha et al., 2014). Ocular dysfunction has been demonstrated up to 3 to 5 months following injury (Heitger, Jones, Macleod, Snell, Frampton, & Anderson, 2009) and is predictive of a longer recovery time (Ventura, Jancuska, Balcer, & Galetta, 2015). Screening for ocular symptoms and impairment following concussion typically involves clinical evaluation of symptoms via patient report or symptom provocation using tools such as the Vestibular/Ocular Motor Screening (VOMS) assessment (Mucha et al., 2014). Although tools such as VOMS have been shown to be sensitive to detect ocular symptoms and impairment following concussion (aside from near point of convergence distance), they rely on subjective symptom reporting. More recently, researchers have begun to employ eye-tracking video oculography devices to measure ocular impairment in concussed patients. A recent meta-analytic review of 21 studies supported post-concussive impairment in oculography-based evaluations of smooth pursuits, self-paced saccades, reflexive saccades, memory-guided saccades, antisaccades, and "fixations" (Snegireva, Derman, Patricios, & Welman, 2018). However, video oculography lacks the reliability and accuracy to measure the smallest FEMS and detect more nuanced, microscopic changes in fixational eye movements that patients may experience following concussion.

Fixational eye movements (FEMs) are involuntary eye movements that keep the eye in constant motion when attempting to maintain gaze on a fixed target (Martinez-Conde, Otero-Millan, & Macknik, 2013). The main components of FEMs are microsaccades and drift. Microsaccades are fast, ballistic movements that are smaller than normal saccades. Although there is no consensus definition on the size cutoff between microsaccades and saccades, microsaccades are typically considered to be on the order of ∼1° to 2° or less in amplitude (Martinez-Conde et al., 2013). Microsaccade kinematics follow the same "main sequence" relationship between amplitude and speed as larger saccades and likely share a common neural oculomotor generator (Goffart, Hafed, & Krauzlis, 2012; Otero-Millan, Troncoso, Macknik, Serrano-Pedraza, & Martinez-Conde, 2008). Drift is the slow, aperiodic motion that occurs between microsaccades. FEMs are task dependent (Rucci & Poletti, 2015) and serve several useful purposes (Rucci & Poletti, 2015; Rucci & Victor, 2015), including enhancing spatial vision (Ko, Poletti, & Rucci, 2010; Ratnam, Domdei, Harmening, & Roorda, 2017; Rucci Iovin, Poletti, & Santini, 2007), and synchronizing sensory and motor neural activity (Greschner, Bongard, Rujan, & Ammermuller, 2002; Leopold & Logothetis, 1998; Poletti & Rucci, 2008). FEMs modulate neural responses in several cortical areas (Hafed, Goffart, & Krauzlis, 2009; Herrington, Masse, Hachmeh, Smith, Assad, & Cook, 2009; Hohl & Lisberger, 2011; Kagan, Gur, & Snodderly, 2008; Martinez-Conde, Macknik, & Hubel, 2000; Rucci & Poletti, 2015; Snodderly, Kagan, & Gur, 2001), and multiple findings support the idea that not only do they contribute to the acquisition of visual information but they are also essential for its processing (Ahissar & Arieli, 2001; Rucci, 2008; Rucci & Poletti, 2015; Rolfs, 2009). FEMs have also been shown to be abnormal in many neurological conditions (Bolger, Bojanic, Sheahan, Coakley, & Malone, 1999; Egaña, Devia, Mayol, Parrini, Orellana, Ruiz, & Maldonado, 2013; Fried, Tsitsiashvili, Bonneh, Sterkin, Wygnanski-Jaffe, Epstein, & Polat, 2014; Gao & Sabel, 2017; Kapoula et al., 2014; Shaikh, Finkelstein, Schuchard, Ross, & Juncos, 2017; Sheehy, Beaudry-Richard, Bensinger, Theis, & Green, 2018; Shirama, Kanai, Kato, & Kashino, 2016). As their spatial scale is on the order of arcminutes, the smallest FEMs require the use of specialized equipment for precise measurement, such as tracking scanning laser ophthalmoscopy (TSLO). TSLO measures eye motion directly by imaging the motion of the retina on a micron scale. TSLO is ideal for capturing the microscopic motion of all FEMs, including the smallest microsaccades (Sheehy, Yang, Arathorn, Tiruveedhula, de Boer, & Roorda, 2012), and may provide a more sensitive and objective assessment of ocular function following concussion.

The purpose of this study was to compare FEMs in patients with a recent concussion (<21 days from injury) to age- and gender-matched controls. Because we were interested in evaluating any difference in FEMs for simple tasks in TSLO that did not require

introducing an additional fixation target, we imaged participants when they fixated both the center of the raster and the corner of the raster and compare the results here. Because no consensus definition of what constitutes a microsaccade exists and we had the capability to measure all of the saccades made during these tasks, we avoid the use of the term "microsaccade" herein and refer to them as "fixational saccades" for the purposes of this report. The TSLO was used to image retinal motion, eye motion traces were computed from the images with high temporal and spatial resolution using custom software (Zhang et al., 2021), and saccades and drifts were segmented for analysis. We also explored potential confounders such as gender, migraine, and previous concussions.

Materials and methods

Participants

A total of 99 adolescents and young adults (13 to 27 years old) participated in the study, including 50 with a diagnosed, symptomatic concussion within the past 21 days recruited from a sports medicine clinic and 49 age and gender-matched healthy controls recruited from a clinical research registry. Participants were excluded if they met any one of the following criteria: history of other neurological and/or psychiatric conditions, vestibular or balance disorders, oculomotor impairment, or ophthalmic conditions; pending litigation; or workers' compensation. Concussion participants were also excluded if they had three or more previous concussions, and controls were excluded if they had a concussion within the last 6 months or reported more than one previous concussion. Participants provided written informed consent (>18 years old) or written informed assent with parental informed consent (<18 years old) prior to initiating study procedures. All aspects of the study were approved by the Institutional Review Board of the University of Pittsburgh prior to participant enrollment.

Measures

Definition of concussion

Concussion was defined per current consensus guidelines based on the following criteria: clear mechanism of injury, presence of one or more signs of injury and/or symptoms at the time of injury, and current symptoms and/or impairment (McCrory et al., 2017). In this study, concussions were diagnosed by licensed healthcare professionals with specialty training in concussion (e.g., clinical neuropsychologists, physicians) based on the preceding criteria per clinical examination and interview, medical/injury history, reported symptoms, and assessments of cognitive, oculomotor, and vestibular impairment.

Fixational eye movements

Image sequences were recorded using a retinal image-based eye tracker, the TSLO (C. Light Technologies, Inc., Berkeley, CA), which is described in detail elsewhere (Sheehy et al., 2012). An 840-nm (50-nm bandwidth) super luminescent diode provided retinal illumination of ~390 μW over a 5° × 5° field of view. To minimize light exposure, the imaging light was modulated at ~15 kHz to be off during the backward portion of each sinusoidal scan, and data were acquired only during the forward scan. A chinrest with temple pads stabilized the head, and image sequences (512 × 512 pixels) were acquired monocularly, from the left eye, without dilation, pixel-by-pixel over time, at a frame rate of 30 Hz. The TSLO, like other devices that use a resonant scanner, requires a sinusoidal rectification (i.e., desinusoiding) to calibrate the scan field and provide a distortion-free image.

Procedures

Most participants completed three fixation tasks, two where they fixated on a portion of the imaging raster (either the center or the corner) and a third, "active" task where they fixated a moving target formed by modulating the raster. The active task will be covered in a subsequent report; the center task was always completed first and the active task last. For the first task, they were instructed to "point your eye to the center of the square" formed by the 5° × 5° imaging raster, which appeared to the participant as a dim red square on a dark background. For the second task, participants were instructed to "point your eye to the upper-right hand corner of the square" (see Figure 1). Though some flicker at 30 Hz is present due to the ramp pattern of the slow scanner, it was not perceptible to the participants because the raster luminance was too low for it to be detected. However, this flicker will modulate the retinal input, and it should be noted that the presence of saccades may render the flicker visible in certain circumstances (Deubel & Elsner, 1986; Kelly, 1990). Fewer participants completed the corner task (n = 90) because it was added to the study protocol after the first nine concussion patients had been imaged in a pilot study. Five 30-second recordings were acquired for each task. The experimenter monitored image quality throughout each recording, and if it became poor during a recording, an additional image sequence was recorded.

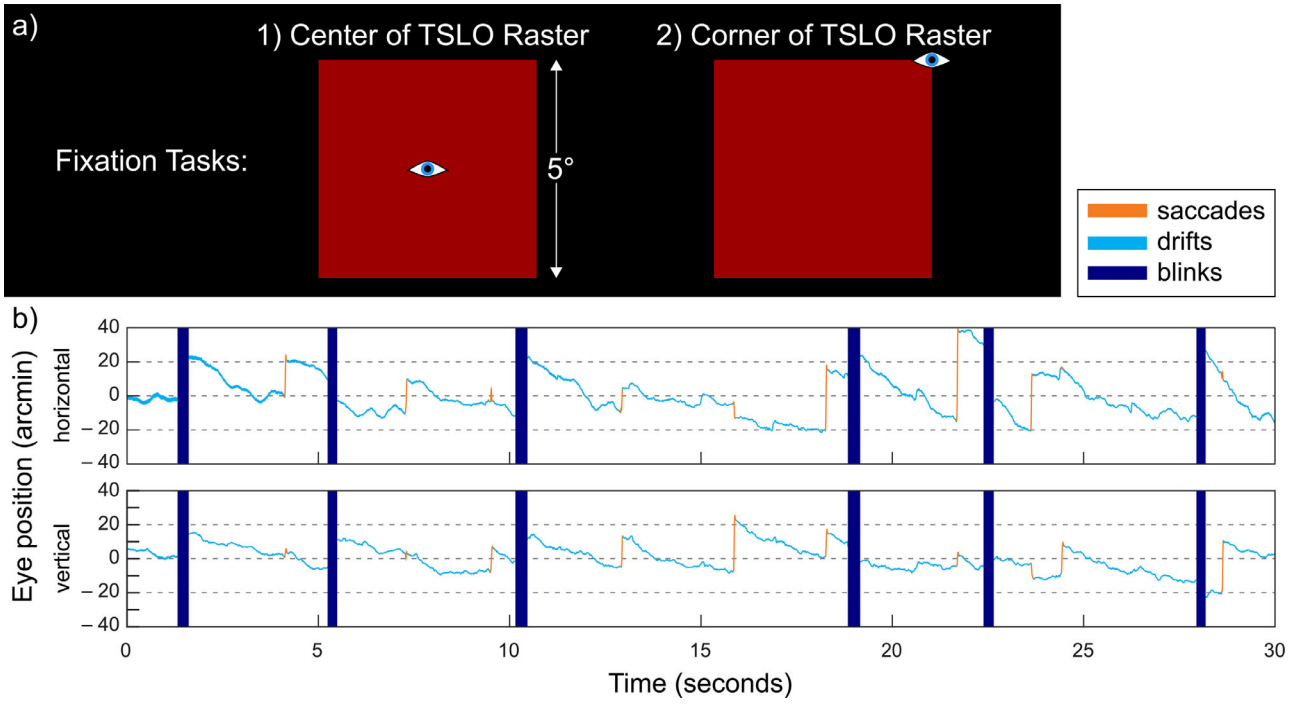

Figure 1. Task overview and representative TSLO fixational eye motion trace segmented into blinks, saccades, and drifts. Upper section shows an illustration depicting each fixation task; position of the eye denotes the fixation location on raster (denoted as red square on black background). Lower plot shows a 30-second eye trace from a single trial from a control participant (RLAB0185) when fixating on the center of the raster. Dark blue rectangles denote the locations of blinks, light blue sections of the motion traces denote drifts, and orange sections denote saccades.

Data analysis

Image processing and eye motion extraction

Eye motion was extracted from TSLO image sequences using custom strip-based image registration and eye motion measurement software that is described in detail elsewhere (Zhang et al., 2021). This approach allows the motion of nearly all frames (~99% after excluding blink frames) to be detected with high spatial and temporal resolution (Zhang et al., 2021). Strip-based fixational eye motion traces were computed using 16 strips per image frame (32 pixels high by 512 pixels wide). Because each individual frame is raster scanned continuously over time, the image-based motion extraction allows much higher temporal sampling than permitted by the slow 30 frames per second frame rate of the imaging system; these strip parameters yield eye traces at a nominal sampling frequency of 480 Hz. Thus, 14,400 eye position measurements are made per 30 second trace (i.e., 30 frames per second × 16 strips per frame × 30 seconds = 14,400 eye position measurements). For the data to be included in our statistical analysis, we set data validation criteria, as follows: (1) >80% of the strips in the image sequence must have been successfully tracked, and (2) three out of five of the image sequences must have met this condition to be included for statistical analyses. The validation criteria were the same for both fixation tasks. Motion traces were generated for both the vertical and horizontal directions. Traces were then reshaped to be 16 × 900 and filtered using a one-dimensional 16th-order median smoothing filter, implemented with the built-in MATLAB function medfilt1 to smooth within-frame motion. Finally, traces were reshaped back to be one dimensional and were filtered by a Gaussian-weighted moving average filter of length 16, implemented using the built-in MATLAB function smoothdata, prior to calculation of the FEM metrics.

Fixational saccades

Candidate saccades were identified using a velocity threshold of 3°/s. Saccade start and end points were set within an interval of one frame (i.e., 33 ms) before and after each detected candidate saccade. Every saccade was individually checked by manual graders to ensure that the beginnings and ends were properly marked; if not, they were corrected manually. When the saccade start and end points had been marked, saccade amplitude, direction, peak velocity, peak acceleration, duration, frequency, and count were computed for each

trial. Saccade speeds reported here are the magnitude of the velocity and acceleration vectors.

Drifts

After saccade and blink segmentation, remaining motion was quantified as drift; however, the period before and after a blink sometimes contained artifactual motion associated with the closing and opening of the eye. We excluded those periods from analysis by detecting the nearest local maximum and/or minimum before and after each blink and removed the intervals between them and the blink start/end. The remaining eye motion was analyzed as drift. A representative, segmented, eye motion trace is shown in Figure 1. We evaluated drift in two different ways and for each trial computed both instantaneous and cumulative drift metrics. To compute instantaneous drift, we simply evaluated all the two-dimensional drift vectors between each datapoint. The length of the vector was taken as the instantaneous drift amplitude, and we divided by the time interval between each datapoint (~2.1 ms) to compute instantaneous drift speed. Average drift amplitude, speed, and direction were computed from these vectors for each trial. For the cumulative drift metrics, we calculated drift speed, variability, and amplitude in the same way as Bijvank, Petzold, Coric, Tan, Uitdehaag, Balk, and van Rijn (2019) and evaluated the horizontal and vertical components separately. The cumulative drift (after removing blinks and saccades) for each trial was fit with a linear regression line. The slope of the regression line fit was taken to be the average drift speed for that trial, and the standard error of the fit was taken to be the drift variability. Drift amplitude was the difference between the start and end point of each trace (Bijvank et al., 2019). The bivariate contour ellipse area (BCEA), defined as the area that encompassed 68% (1 *SD*) of the two-dimensional position of each trace, was calculated to determine spread of fixation.

Fatigue

Because it is conceivable that participants may have experienced some fatigue or boredom after fixating for more than 10 seconds during each 30-second trial and perhaps started to look around at the edges of the raster, we also evaluated fixational saccade amplitude within each trial. For this analysis, we divided each trial into three temporal epochs, consisting of the first, second, and third 10-second intervals, and then averaged the amplitude of the saccades measured in each interval for the five trials in each condition. Our hypothesis was that we would not see any difference in saccade amplitude when comparing the different intervals. However, if there was an effect of fatigue, we would expect saccade amplitude to be smallest in the first 10-second interval and increase in the subsequent two intervals.

Statistical analysis

Injured and non-injured participant groups were compared for demographic and medical history characteristics as appropriate for mean differences (*t*-test or Mann–Whitney *U*) or proportions of categorical variables (contingency table with chi-square or Fisher's exact test). All FEM parameters were screened for normality. A log-normal transformation was applied to parameters if non-normally distributed prior to injury-control group means comparisons using parametric methods. If a normal distribution was not found with transformation (Kolmogorov–Smirnov $p < 0.05$), between group mean comparisons were performed using non-parametric methods. A multivariate generalized linear model was conducted on both fixation tasks with injury group, gender, and potential confounders (migraine; prior injury history) with possible interactions as fixed between-group factors. When a significant multivariate trend (at $p < 0.05$) was found across parameters, individual parameter group mean differences were tested using the independent sample *t*-test or two-way analysis of variance, depending on the significance of a confounder effect in multivariate analysis. Between-group effects on parameters where transformation did not conform to normality were tested using a non-parametric, two-sample Mann–Whitney *U* test. Consistency of task performance across three temporal intervals for each trial was evaluated by interclass correlation coefficients using a two-way analysis of variance model for mean interval amplitude. The accuracies of the significant average fixational saccade parameter values (i.e., amplitude, velocity, and acceleration) for all participant data were combined to identify injured participants using a receiver operating characteristic (ROC) area under the curve (AUC) against a null hypothesis of AUC = 0.5. Significant curves were identified at $p < 0.05$. Analyses were performed using SPSS Statistics 25 (IBM Corporation, Armonk, NY).

Results

Data from 88 of the 99 (89%) total participants met the validation criteria for at least one of the two fixation tasks. Demographics for the overall sample of concussed and control participants are provided in Table 1. Data from 84 of the 99 total participants (85%) met the validation criteria for inclusion outlined above for the center-of-raster fixation task; for the corner-of-raster fixation task, 67 of 90 participants

Variable	Concussion ($n = 44$)	Healthy ($n = 44$)
Age (y), mean ± SD	16.9 ± 3.2	17.0 ± 3.2
Female, *n* (%)	24 (55)	24 (55)
Concussion history, *n* (%)	14 (32)	8 (18)
Motion sickness history, *n* (%)	10 (23)	7 (16)
Migraine history, *n* (%)	13 (30)	4 (9)

Table 1. Participant demographics.

(75%) met the validation criteria. Concussed and control participants were similar on all demographic and medical history variables. The primary mechanisms of injury among concussed participants were sport or recreation related (45%, $n = 20$) and due to motor-vehicle collisions (16%, $n = 7$). On average, concussed participants were 12.85 days ($SD = 4.88$) from injury and reported total concussion symptom severity scores (from the Post-Concussion Symptom Scale) of 35.6 ($SD = 24.6$; possible range of 0–132).

Peak velocity versus amplitude values for each individual saccade from each group and task are plotted in Figure 2. These plots showed a linear relationship between saccade amplitude and peak velocity (i.e., they followed the main sequence); linear regression lines fit to the data for each group were nearly identical. The histograms in Figure 2 show fixational saccade

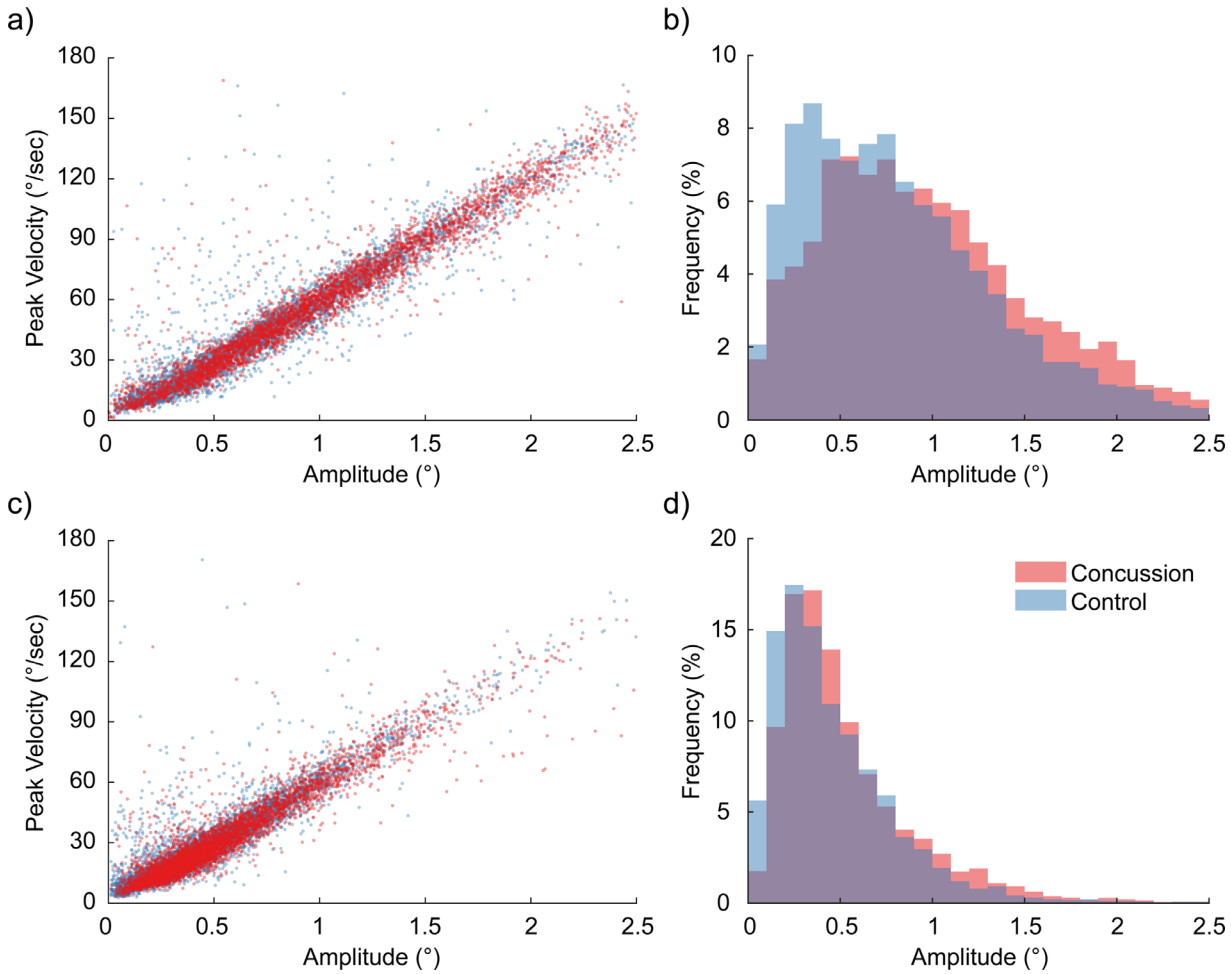

Figure 2. Main sequences and histograms for each task. Saccade main sequence plots for both the concussion (red) and control (blue) groups show a linear relationship between saccade peak velocity and amplitude for both the center-of-raster fixation task (a) and the corner-of-raster fixation task (c). Histograms for both the center (b) and corner (d) fixation tasks show substantial overlap in distributions across the different amplitudes, but in both cases the concussion group saccades show a trend toward a greater proportion of larger amplitude saccades compared with controls. Note that data points in the main sequences have been made partially transparent to allow for color saturation to demonstrate data density but that with the thousands of points shown here many are obscured; the purple regions in the histogram plots denote overlap of the distributions. For clarity across the majority of saccade amplitudes, the amplitude and velocity axes in (a) and (c) are set at a cutoff that excludes a small proportion of larger saccades (>2.5°); these represent only a tiny fraction of the data (center task, 3.5% for concussion and 1.4% for controls; corner task, 0.09% for concussion and 0.21% for controls).

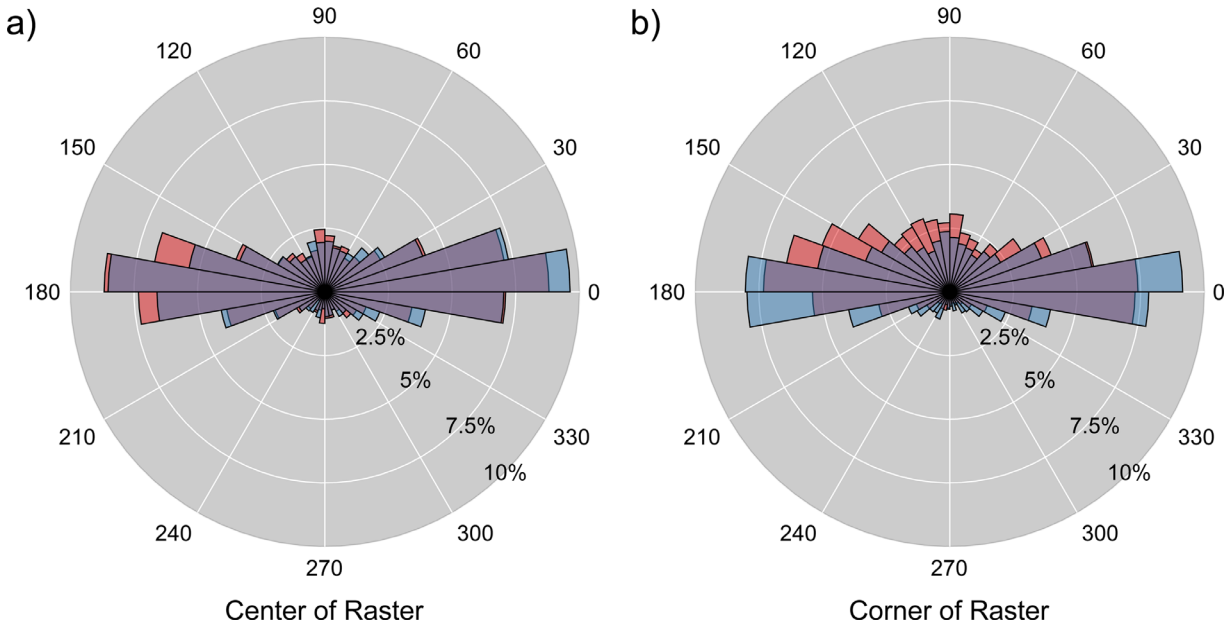

Figure 3. Fixational saccade direction histograms for all fixational saccades made in each task. Histograms for both the center (a) and corner (b) fixation tasks for the concussion group (red) and controls (blue) show substantial overlap (purple) across the different directions. Although the pattern of the direction distribution appears similar in both tasks for controls, the concussion group directionality pattern appears to differ between tasks, with a larger proportion of vertical and oblique saccades made in the corner task (b) compared with the center task (a); however, group means were not statistically different.

amplitude distributions for each group and task. The histograms indicate that these distributions had substantial overlap between groups for both tasks but that in both cases the injured participant distributions showed a trend toward having larger saccades compared with the control group. Polar histograms are provided in Figure 3 to show the distribution of fixational saccade directions for each group and task. These also show substantial overlap, but some differences were observed; although controls showed similar directionality distributions in both tasks, the concussion group's direction distribution appeared less similar between tasks. Injured participants made a larger proportion of vertical and oblique saccades when fixating the corner of the raster compared with the center.

Summary statistics for fixational saccade amplitude, peak velocity, and peak acceleration for each group are plotted in Figure 4. Statistical analyses showed that individual mean parameter comparisons for the center-of-raster fixation task demonstrated significantly increased amplitude ($t = 2.89$, $df = 82$, $p = 0.005$) in concussed participants compared with controls (minimum effect size of difference = 0.63) (Table 2). These saccades followed the main sequence (see Figure 2) and showed significantly greater peak velocity ($t = 2.82$, $df = 82$, $p = 0.006$) and peak acceleration ($t = 2.83$, $df = 82$, $p = 0.006$) compared with controls (effect size of difference = 0.62).

There was a significant multivariate effect of injury group on mean fixational saccade amplitude, peak velocity, and peak acceleration ($F = 2.77$, $df = 3$, $p = 0.047$, residual normality $p > 0.20$) when participants fixated on the center of the raster. There were no significant between-group effects of gender ($F = 0.251$, $df = 3$, $p = 0.861$), previous concussion ($F = 038$, $df = 3$, $p = 0.990$), or migraine history ($F = 1.83$, $df = 3$, $p = 0.148$) in a multivariate model with injury group. Fixational saccade parameters of amplitude (AUC = 0.68, $p = 0.005$), peak velocity (AUC = 0.67, $p = 0.006$), and peak acceleration (AUC = 0.67, $p = 0.008$) significantly differentiated concussed from healthy control subjects in the center-of-raster fixation task (Figure 5). There were no effects of concussion on fixational saccade amplitude ($t = 0.384$, $df = 65$, $p = 0.702$), peak velocity ($t = 0.212$, $df = 65$, $p = 0.833$), or peak acceleration ($t = 0.206$, $df = 65$, $p = 0.838$) in the corner-of-raster fixation task.

When splitting up each 30-second trial into three, 10-second epochs, fixational saccade amplitude showed no increase with time (see Figure 6). Amplitude reliability analysis for the three intervals were as follows: center of raster concussion group, ICC = 0.611; center of raster controls, ICC = 0.579; corner of raster concussion group, ICC = 0.709; and corner of raster controls, ICC = 0.619. Hence, 58% to 71% of the variance was due to the difference between subjects

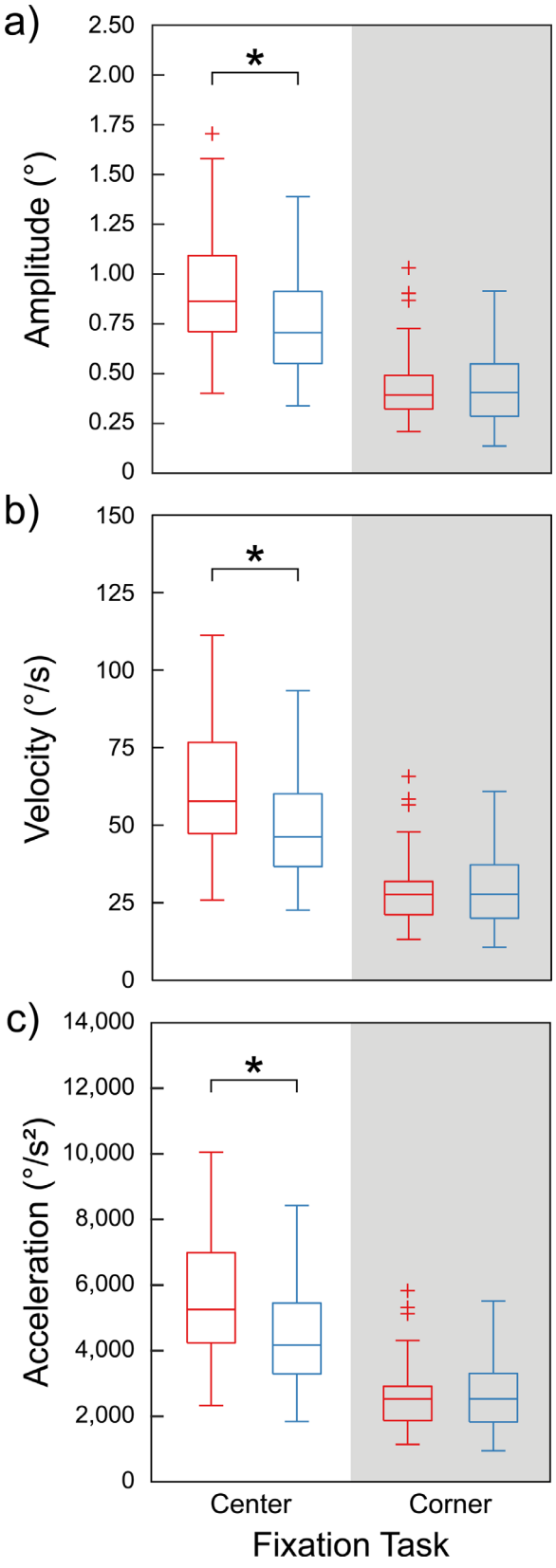

Figure 4. Comparison of fixational saccade parameters between groups and tasks. Box and whisker plots compare the fixational saccade statistics computed for each group. When fixation was on the center of the raster (left; white background) the amplitude (a), velocity (b), and acceleration (c) of fixational saccades were significantly different between groups. No metrics were significantly different between groups when fixation was on the corner of the raster (right side, shaded background). *Statistically significant group means (see Table 2).

within each interval, and only 29% to 42% of the variance was due to the difference between intervals, within subjects. No significant within-subject difference by interval was seen on repeated-measures analysis for either the center-of-raster or corner-of-raster task.

Discussion

This is the first study to demonstrate differences in fixational saccades, as measured using high-resolution retinal image-based eye tracking, between patients with a recent concussion (≤21 days) and controls. Patients with concussion demonstrated significantly greater mean fixational saccade amplitude compared with age- and gender-matched controls when fixating on the center of the imaging raster but not when fixating on the corner of the raster. Because these fixational saccades made by concussed patients followed the same main sequence relationship for saccades that has been well-established for normal observers, their velocities and acceleration were also significantly different (Table 2).

It has been shown that fixation target size, color, and luminance can all affect fixation (McCamy, Najafian Jazi, Otero-Millan, Macknik, & Martinez-Conde, 2013; Steinman, 1965), with recent evidence demonstrating that microsaccade magnitude increases linearly with target size (McCamy et al., 2013). When participants fixated a small, well-defined point in space (i.e., the point where the edges of the raster meet), there were no statistically significant differences found in the fixational saccade statistics between the concussion group and the controls. We did see some trends in the concussion group for that fixation task toward larger amplitude saccades (see Figure 2) and some differences in the distribution of saccade directions (see Figure 3), but the group difference was not significant. However, when the entire 5° × 5° imaging raster was used as the fixation target, the concussion group's fixational saccades had greater amplitude. Because we were able to measure all of the saccades made during these fixation tasks with TSLO, including the smallest fixational saccades, we did not set an arbitrary amplitude cutoff to consider the smallest ones to be "microsaccades" and the larger ones to be "saccades." A major shortcoming of the state of this field is that the definition of what a microsaccade is lacks consensus in the literature and can be based on

	Task					
	Fixation on center of raster ($n = 84$), mean (SD)			Fixation on corner of raster ($n = 67$), mean (SD)		
Group	Concussed ($n = 42$)	Healthy ($n = 42$)	p	Concussed ($n = 33$)	Healthy ($n = 34$)	p
Saccade duration (s)	0.064 (0.006)	0.066 (0.006)	0.307	0.067 (0.007)	0.068 (0.007)	0.437
Saccade direction (rad)	0.892 (1.43)	1.04 (1.32)	0.788	1.204 (1.2)	1.058 (1.48)	0.763
Saccade peak velocity (°/s)	61.54 (21.18)	49.54 (18.51)	0.006*	30.14 (21.31)	29.96 (12.26)	0.833
Saccade peak acceleration (°/s^2)	5351.03 (1921.20)	4456.81 (1680.52)	0.006*	2685.87 (1122.70)	2668.10 (1117.93)	0.838
Saccade amplitude (°)	1.03 (0.36)	0.82 (0.31)	0.005*	0.500 (0.216)	0.480 (0.200)	0.990
Cumulative drift speed, horizontal (°/s)	0.126 (0.105)	0.121 (0.099)	0.986	0.129 (0.134)	0.101 (0.069)	0.990
Cumulative drift speed, vertical (°/s)	0.065 (0.041)	0.0901 (0.069)	0.077	0.053 (0.040)	0.071 (0.054)	0.164
Cumulative drift amplitude (°)	3.99 (2.56)	4.27 (2.48)	0.485	3.71 (3.17)	3.19 (1.76)	0.841
Cumulative drift variability, horizontal (SE)	0.34 (00.26)	0.30 (00.25)	0.267	0.29 (0.287	0.23 (0.17)	0.950
Cumulative drift variability, vertical (SE)	0.32 (00.17)	0.34 (00.21)	0.782	0.25 (0.13)	0.24 (0.14)	0.310
Instantaneous drift direction (rad)	–0.68 (1.78)	–0.94 (1.77)	0.192	–1.22 (1.37)	–1.10 (1.54)	0.861
Instantaneous drift speed (°/s)	0.935 (0.196)	1.04 (0.396)	0.734	0.876 (0.218)	0.895 (0.251)	0.744
Instantaneous drift amplitude (°)	0.0019 (0.0004)	0.0022 (0.0008)	0.687	0.0018 (0.0005)	0.0019 (0.0005)	0.730
BCEA (°^{2})	1.43 (1.00)	1.17 (0.79)	0.256	0.28 (0.25)	0.27 (0.19)	0.635

Table 2. Fixational eye movement statistics in concussed and healthy controls compared for the two different fixation tasks. *Denotes significance of independent samples (*t*-test or non-parametric) group effect comparison.

several factors aside from their size (Poletti & Rucci, 2016). We chose to examine all of them here so as not to bias our results. For example, had we only examined the tiniest microsaccades (e.g., those less than 0.5°) we would have been evaluating only a small fraction of the data in the center-of-raster fixation task, as only 22% of all of the saccades made fell into that size range for the concussion group; the proportion was greater for the controls but still only represented 33% of all the saccades. The proportion less than 0.5° in amplitude was substantially different for the corner-of-raster fixation task, representing 60% of all saccades for the concussion group and 64% for the controls. We consider this to be an important finding, as it suggests that eye trackers whose resolution cannot detect microsaccades smaller than 0.5° might miss nearly two-thirds of all the fixational saccades made when fixation is directed to relatively small targets.

The current findings regarding fixational saccades following concussion support and extend previous findings involving larger amplitude saccades as measured by eye-tracking (Murray, Szekely, Islas, Munkasy, Gore, Berryhill, Reed-Jones, 2020) and from clinical findings on tools such as the VOMS (Kontos et al., 2021). Researchers suggest that ocular dysfunction following concussion may result from transient disruption of the neural pathways in the brain associated with eye movements (Johnson, Hallett, & Slobounov, 2015; Kellar, Newman, Pestilli, Cheng, & Port, 2018). However, oculomotor impairments can often be difficult to detect due to the subtlety in presentation of the injury in some patients and may require more sensitive tools to detect as demonstrated in recent case reports (Cochrane, Gould, Sheehan, Busettini, Christy, Weise, & Swanson, 2020). As such, a detailed assessment of FEMs may help augment current approaches including video oculography or clinical observation.

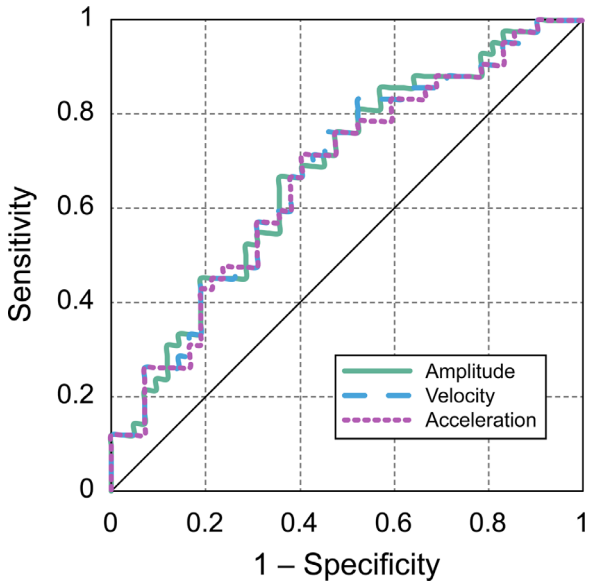

Figure 5. Receiver operating characteristic curve for accuracy of fixational saccade metrics to identify subjects with concussion. When fixation was on the center of the raster, fixational saccade parameters significantly differentiated concussed from controls (AUC = 0.67–0.68; minimum $p = 0.005$).

Currently, ocular dysfunction following concussion is evaluated using clinical examination and tools such as VOMS (Mucha et al., 2014). However, with the exception of the measurement of near point convergence distance, VOMS focuses on patient-reported symptom provocation. Although previous researchers have subsequently identified

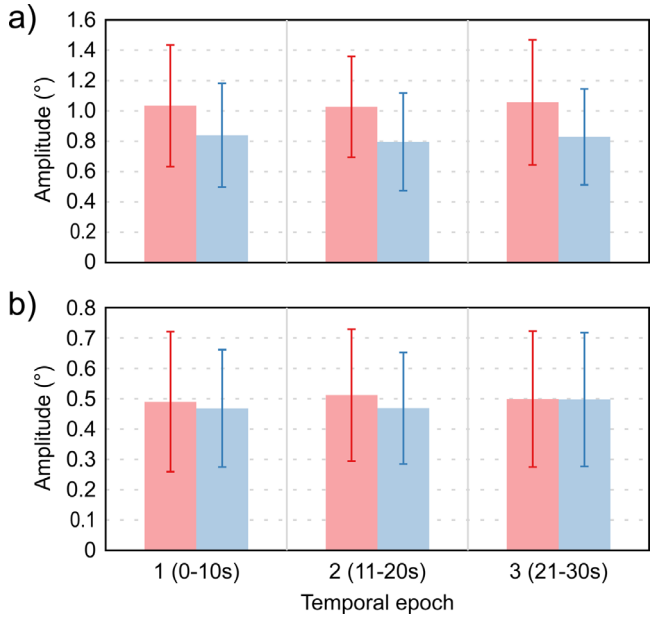

Figure 6. Fixational saccade amplitude did not increase across each 30-second trial. Fixational saccade amplitudes were averaged using only the first, second, or third 10 seconds of each eye position trace to evaluate the presence of fatigue that might be rendered as an increase in amplitude across time. Fixational saccade amplitudes were nearly identical across the different temporal epochs evaluated for each group in both the center (upper) and corner (lower) fixation tasks. The concussion group is shown in red and control in blue; error bars are $\pm SD$.

gross ocular impairments using video oculography, this body of research has several limitations worth considering, including lack of pre-injury or matched control group performance for comparison, calibration, and resolution issues, as well as the inability to address confounding factors such as attention and medication (Ventura et al., 2015). The results of the present study suggest that TSLO measurement of FEMs during a fixation task with a relatively large stimulus (i.e., larger than the fovea) is sensitive enough to detect subtle ocular impairments. As such, FEMs as measured using TSLO could provide an objective evaluation of ocular dysfunction to augment current clinical tools and inform recommendations for ocular therapy. The task-dependent differences seen here warrant further investigation and suggest that there may be other fixational tasks that better distinguish concussed patients from controls; future studies should explore this possibility.

We can only speculate as to the mechanistic underpinnings driving the deficits we detected here in concussed patients. Evidence from years of primate neurophysiology studies suggests that fixation in the brain is mediated by the deep superior colliculus (dSC). It has been proposed that fixation control arises through population coding in the dSC (Goffart et al., 2012). An equilibrium model of dSC control has been proposed based on the results of dSC inactivation experiments in monkeys that suggest that fixation is an equilibrium established by the population average of fluctuating target position signals issued bilaterally from the two deep superior colliculi (Goffart et al., 2012). These dSC inactivation studies also showed that larger fixation offsets were seen for larger fixation targets after dSC inactivation (Goffart et al., 2012), supporting the hypothesis that larger target sizes expand the population of active dSC neurons during fixation (Goffart et al., 2012; Hafed & Krauzlis, 2012). Within this framework, our center-of-raster fixation task would engage a larger population of active dSC neurons during fixation compared with the corner-of-raster fixation task. It is conceivable that injury from concussion introduces some errors or noise into the target position signals encoded by individual neurons. The cumulative effect of errors or increased noise in the population average of fluctuating target position signals of active dSC neurons may be greater for larger populations of cells compared with smaller ones—for example, if the effect of the noise or positional errors is multiplicative rather than additive. However, much more work is needed to understand the mechanisms driving the results seen here, because concussion may also alter other aspects of the fixational control network that is responsible for transporting the multisensory encoded signals from the dSC to the reticular formation in the brainstem and ultimately to the extraocular muscles.

Limitations

Although testing and setup are quick, and eye traces can be extracted with high precision (Zhang et al., 2021), the saccade segmentation process must be streamlined. Because this was a preliminary study, we included patients with and without concussion-related ocular dysfunction or symptoms (per VOMS and clinical exam findings). Therefore, the AUCs in the current study were in the acceptable range (i.e., AUC = 0.7), whereas they may be higher for identifying patients specifically with ocular dysfunction or symptoms. The task specificity revealed here suggests that task optimization might also improve sensitivity. Recent work suggests that fixational stability may be used to differentiate patients with mild traumatic brain injury from controls in a pediatric population (Hunfalvay, Murray, & Carrick, 2021). Future research should evaluate the ability of FEMs to identify patients with ocular dysfunction or symptoms following concussion, which could provide objective data to complement current symptom-based tools (e.g., VOMS).

Conclusions

This study is the first, to the best of our knowledge, to demonstrate that patients (ages 13–27 years) with a recent concussion (≤21 days) have altered fixational saccades compared with controls. Fixational saccades significantly differentiated concussed patients from healthy controls when fixating on the center of the raster. These results suggest that FEM measurement in the acute to subacute period of concussion recovery may provide a quick (<3 minutes), objective, sensitive, and accurate assessment of ocular dysfunction. Such an assessment may offer clinicians a more rapid and objective test of oculomotor function following concussion than current approaches involving subjective symptom reporting or pupil-based eye tracking. Future work is necessary to evaluate task specificity, age differences, and prospective changes in FEMs across recovery, as well as to develop rapid post-processing techniques to facilitate clinical use.

Keywords: fixational eye movements, microsaccades, concussion, scanning laser ophthalmoscopy, eye motion measurement

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Commercial relationships: none.
Corresponding author: Ethan A. Rossi.
Email: rossiea@pitt.edu.
Address: Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

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