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Vergence Endurance Test:
A Pilot Study for a Concussion Biomarker

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Abstract

The Vergence Endurance Test (VET), a quantitative and objective eye movement assessment, was utilized to differentiate control from concussed subjects. Nine symptomatic concussed (2 male; 30.8 ± 11 years) and 9 asymptomatic control (6 male; 25.1 ± 1.4 years) subjects participated in the VET. Symmetrical disparity vergence step targets were presented with and without visual distractors. A masked data analyst measured vergence latency, peak velocity, response amplitude, settling time, and the percentage of trials which contained blinks. A Binocular Precision Index (BPI) and a Binocular Accuracy Index (BAI) were calculated to quantify the changes that occur in the vergence parameters over the duration of the VET. Convergence and divergence peak velocity, divergence response amplitude, the percentage of trials that contained blinks during the transient portion of the response, and the BAI were significantly ($p < 0.05$) different between the concussed and the control subjects. For these parameters, the BAI and divergence response amplitude yielded the greatest accuracy, 78%, in their ability to discriminate between the groups. The VET objectively measures the change in vergence performance over time and shows promise as a method to diagnose a concussion. Future studies will determine whether the VET can be used to assess the extent of natural recovery and the effectiveness of therapeutic interventions.

Keywords: concussion biomarker; objective concussion metric; post-concussion syndrome; vergence distractors; vergence eye movements

Introduction

Concussion has been defined as a "… complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces."[1] It has been referred to as an epidemic health problem.[2–4] According to studies from BlueCross BlueShield between 2010 and 2015, the prevalence of concussion diagnosis has increased by 71% in the 10- to 19-year-old age group.[5] While some symptoms resolve during natural recovery and rest, a longitudinal study showed that 41% of the 591 concussed patients studied were classified as having post-concussion syndrome (PCS) where symptoms did not dissipate after 2 weeks.[6] Another study reports that 46% of the 2946 enrolled children had a diagnosis of PCS 2 weeks post-injury, which decreased to 33% 4 weeks post-injury.[7]

Concussions are associated with diffuse axonal injury within the brain.[8] Hence, it is not surprising that a variety of symptoms are common, including dizziness, headaches, inability to sustain attention during a long duration task, fatiguing faster post-injury compared to pre-injury, loss of memory, and blurry/double vision.[2,9–11] Eye movements performed for a prolonged period of time have been reported to evoke visual fatigue.[12,13] A quantitative test that could assess dysfunction associated with attention and fatigue in concussion would be beneficial. Several studies report abnormalities in convergence, accommodation, the vestibulo-ocular reflex, ocular muscle balance, saccade, and smooth pursuit in those with concussion compared to controls and recommend the use of eye trackers and pupillometry to objectively measure the amount of dysfunction.[14–23] One study specifically suggests using an oculomotor attention-based test as a biomarker for concussion.[24]

Changes in oculomotor peak velocity and final amplitude occur when a healthy control subject tracks a target in the presence of distracting visual stimuli during a 1-h vergence eye movement task leading to visual fatigue.[25] The primary aim of this study is to determine whether patients with concussion demonstrate findings of more significant levels of visual fatigue than healthy controls. This study seeks to determine whether utilizing eye movement testing,[15,26] as in the Vergence Endurance Test (VET), may serve as a potential biomarker for concussion.

The diagnosis of concussion is challenging for clinicians because it is based largely on the reported mechanism of injury and subjective patient self-disclosed symptoms.[27] Symptom information may be captured using the Post-Concussion Symptom Scale (PCSS)[28] or the Brain Injury Vision Symptom Survey (BIVSS).[29] There has been a lack of solid objective measures in concussion diagnosis and heavy reliance upon subjective symptom surveys

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such as the PCSS and the BIVSS[29] or cognitive tests such as ImPACT[28] and SCAT5.[30] Yet, these symptom assessments have challenges because they are subjective and depend on a patient's response by design. Most of these assessments are also dependent on pre-athletic season baseline data, which may not always be available or accurate. Concussion diagnosis would benefit from more objective assessments to corroborate symptoms.

The 2016 Berlin Consensus of Concussion states that for sports-related concussion (SRC), there is "… no perfect diagnostic test or marker that clinicians can rely on for an immediate diagnosis of SRC."[27] There is a clinical need for diagnostic biomarkers that utilize more objective means to assess the presence of concussion especially tests that are not dependent on baseline measurements. This investigation is designed to establish an objective and quantifiable method to detect a concussion and, in the future, assess the concussion severity and potentially predict which people will experience prolonged symptoms.

Studies have demonstrated that binocular vision dysfunction is common after concussion and associated with characteristic symptoms.[17,31–33] In one study, the PCSS demonstrates that 70.4% of 260 concussed athletes report visual disturbances, which is the seventh most frequently reported symptom.[34] This investigation is designed to determine whether changes in vergence eye movements during a sustained demanding visual task (a task which presents distracting stimuli) can serve as a potential objective, quantitative biomarker in concussion. This experiment tests the hypothesis that compared to asymptomatic healthy control subjects, symptomatic concussed subjects will exhibit greater degradation in vergence eye movement accuracy and precision during an 18-min VET. In other words, compared to healthy control subjects, concussed subjects will exhibit less visual endurance.

Methods

Subjects

The data for this research were collected at the Clinical Research Center at The Eye Institute of the Pennsylvania College of Optometry at Salus University (Elkins Park, PA) by an optometrist, one of the co-authors (L.G.). Healthy control subjects and test subjects with PCS were recruited from the local area. Average time since concussion was 6.5 months with a standard deviation of 3.1 months and a range of 3.0–12.5 months. Nine concussed (2 males) and 9 neurologically normal controls (6 males) participated. Average age was 30.8 ± 11 years for concussed subjects and 25.1 ± 1.4 years for controls. All subjects provided written informed consent before the experiments, which was approved by the Salus University's Institutional Review Board in accord with the Declaration of Helsinki. A history of past brain injury or concussion(s) was an exclusion criterion for the control group. Using standard subjective refraction methods, all subjects were refracted to best visual acuity with maximum plus. One concussed subject was a mild hyperope (1D OS, 0.75D OD), and 6 myopes were in the control group. No subject had refractive error more than −6D.

Subject symptoms and clinical visual measurements

Symptoms were measured using the PCSS and BIVSS for both controls and concussed subjects. The PCSS contains 22 questions to assess symptoms such as headache, fogginess, and dizziness.[35] The PCSS uses a 0- (no symptom) to 6-point (severe symptom) Likert scale. Hence, the PCSS maximum possible score is 132. Normative data report that 89% of healthy control subjects report a 12 or lower on the PCSS while the average PCSS score for those with a concussion is 24.[34] For this study, symptomatic is defined as reporting a PCSS score of ≥12. The BIVSS is a 28 self-administered query that assesses vision-related behaviors, including reading, light sensitivity, peripheral vision, dry eye, depth perception, diplopia, and eyesight clarity.[29] The BIVSS uses a 5-point Likert scale of never, seldom, occasionally, frequently, and always which are recorded from 0 to 4, respectively. The highest possible score of the BIVSS is 112. Subjects who did not have survey scores are listed as not available (N/A).

Experimental setup

Eye movements were quantified with ISCAN infrared ($\lambda = 940$ nm) video-based cameras placed 38 cm away from the subject's midline per the manufacturer's recommendation. Each camera sampled at 240 frames per second. Left and right eye movements were collected independently.[36–39] Visual stimuli were presented on a traditional haploscope (Fig. 1A). Subjects were centered in front of two partially reflective mirrors where each mirror displayed the respective image

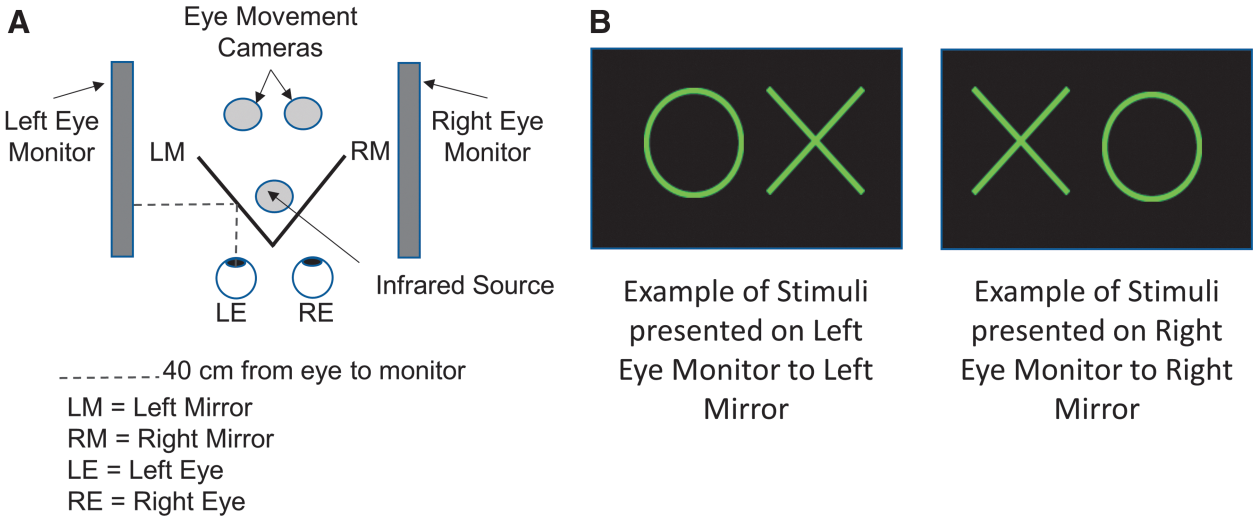

FIG. 1. (**A**) Haploscope experimental setup showing how the subject was positioned. All visual stimuli are presented on the midsagittal plane. (**B**) Visual stimuli presented to the left and right eye. The X is the instructed target to follow, and the O is the distractor that may or may not be presented during an experimental trial.

from the monitor. Visual stimuli (Fig. 1B) to the left and right eye were presented centered along the midsagittal plane.

This experimental setup and instrumentation was identical to other studies.[40–45] The subject was seated in an enclosed space with commercial blackout curtains to reduce proximal vergence cues. The entire system was controlled by a custom LabVIEW™ 2013 SP 1 Virtual Instrument (National Instruments, Austin, TX) program VisualEyes2020 (VE2020), which digitizes the eye movement signals using 16 bits.[46]

Experimental design

Two 1-min calibrations were recorded. The calibration sequences consisted of six observations of monocular targets at 1, 3, and 5 degrees lateral to midline for each eye. This 6-point monocular calibration minimizes errors, which could potentially be introduced because of fixation disparity.[47] Binocular convergence and divergence demands which abruptly shift between 6 and 10 degrees were chosen for this experiment because 4-degree vergence steps elicit fewer saccadic responses compared to larger vergence movements of 6-degree vergence steps or more.[48–53] Visually demanding stimuli were presented in the presence of other distracting visual stimuli. Stimuli were chosen based upon a previous detailed study from our laboratory.[54]

In this study, we utilized six vergence stimuli with distractors and two distractor-free vergence stimuli for a total of eight types of vergence eye movement stimuli. The subject was instructed to fixate on the green "X" (called the "instructed target"). The subject was also instructed not to fixate on the green "O" (called the "distractor stimulus"). Both the X and O visual stimuli subtended an angle of 1.5 degrees in width and height against a homogenous black background (Fig. 1B). The distractor-free testing sequence is demonstrated in Figure 2A. The stimulus begins at a binocular 6-degree angle of convergence demand—and abruptly changes to a 10-degree angle of convergence demand. In other words, this stimulus is analogous to a clinician holding two targets along a patient's midsagittal plane and asking them to quickly alternate fixation between the closer and further target. The subject then perceives a net 4-degree symmetrical convergence disparity stimulus along the midsagittal plane. Similarly, we define divergence stimuli as those that begin at 10-degree convergence angular demand and end at 6-degree convergence angular demand, which is a net 4-degree change of relative divergence disparity.

The same 4-degree convergence and 4-degree divergence step used within the distractor-free stimuli were presented for the stimuli that contained distractors. Note how the red line in Figure 2 (the instructed target) is the same in Figure 2A–D. However, in addition to a green X, a green O was also presented in Figure 2B–D. The O appeared at an angular convergence demand of either 4, 8, or 12 degrees. Convergence and divergence 4-degree steps (where the instructed X targets were presented) also had the distracting O stimuli presented at a maximum or minimum distance from the instructed target (Fig. 2B,C, respectively). The last visual stimulus paradigm had the visual distractor placed consistently at 8 degrees, which is midway between the 6- and 10-degree convergence angular demands of instructed targets (Fig. 2D). We define this as the in-between response.

Stimuli were presented in 24-sec blocks; the distractor O was only presented to the subject for 1.5 sec after each convergent or divergent step of the instructed target X (see Fig. 2). The 24-sec block was presented six times each see (Fig. 2E). There were 24 presentations of each stimulus within the experiment or 192 eye movement responses per subject. The four target/distractor group combinations (Fig. 2A–D) were presented randomly three times each to form one bin (Fig. 2E). There were two bins in total (24 sec for each visual paradigm for a total of 576 sec per bin). The total experiment was around 18 min in duration. The duration of 18 min was selected to model other endurance stress tests, which last between 15 and 20 min.[55] Calibration was around 2 min in duration for a total of 20 min of testing. After calibration was explained and performed, all subjects were instructed to keep the letter X single and ignore the distracting letter O when it appeared.

Eye movement data analysis

The data analyst was masked to the subject type (i.e., asymptomatic control or symptomatic concussed subject) during basic analysis to avoid any bias or skewing of results. Only when specificity, sensitivity, and accuracy were calculated was the data analyst aware of the subject type.

Vergence eye movements were calibrated using the monocular calibration values. Vergence position was calculated by subtracting the right- and left-eye positional data (in degrees), where convergent eye movements were plotted as positive. Individual vergence eye movement data were filtered using a second-order low-pass Butterworth filter with a cut-off frequency of 40 Hz. The following metrics were obtained from each individual vergence eye movement response: 1) latency, 2) settling time, 3) peak velocity, and 4) response amplitude. Response latency was obtained by measuring the time when the vergence eye position increased from the initial vergence angle by an increment of 10% of the total stimulus movement. Hence, for this study that meant 0.4 degrees (see Fig. 3). Settling time was obtained by finding the time at which the vergence eye position fluctuated by <5% of the responses steady state. Final response amplitude of the vergence eye movement was measured as the difference between the final and initial vergence angular demands (see Fig. 3). A two-point central difference algorithm was used to compute the vergence velocity response.[56] The maximum of the velocity was measured.

Percentage of trials of the total of 192 movements that contained blinks was tabulated. Past research on perceptual and cognitive tasks report that the number of blinks increases as a function of the duration of task time and suggest that blinks are associated with general fatigue.[57] A blink is easily identified because the eye movement signal saturates (measured as a maximum value possible within our system). A blink is counted in an eye movement response between the latency and settling time of the movement.

Binocular Accuracy Index and Binocular Precision Index

The following two new metrics were developed to evaluate visual endurance: the Binocular Accuracy Index (BAI) and the Binocular Precision Index (BPI). Gain is a standard engineering term defined as the output divided by the input. For our application, it is the response amplitude (output) divided by the visual stimulus (input) for this application. Error is the difference between the final eye movement response and the instructed visual stimulus. Precision is a quantification of the variability between observations and is also known as the repeatability. For this study, precision is the

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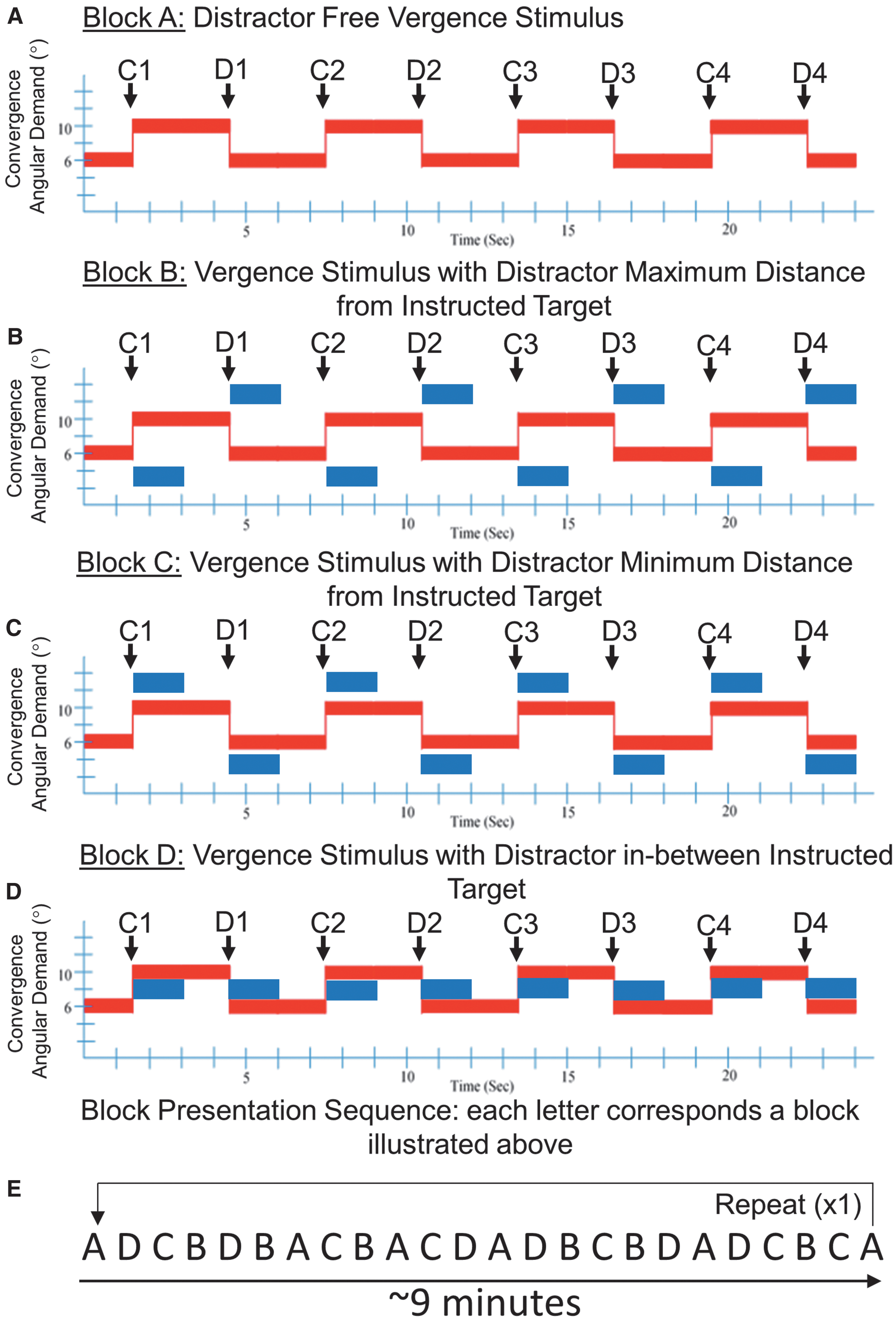
FIG. 2. Vergence stimuli showing the instructed target (red line) and the distracting target (blue line) presentation. (**A**) Distractor-free stimulus. (**B**) Visual stimulus when the distractor was the furthest away from the instructed vergence stimulus. (**C**) Visual stimulus when the distractor was the closest to the instructed vergence stimulus. (**D**) Visual stimulus when the distractor was in between the convergence and divergence stimulus. Presentation locations are denoted in binocular angular convergence demand (degrees) as a function of time (seconds). (**E**) Overall experimental sequence.


A
Block A: Distractor Free Vergence Stimulus
C1
D1
C2
D2
C3
D3
C4
D4
Convergence Angular Demand (°)
10
6
5
10
15
20
Time (Sec)
Block B: Vergence Stimulus with Distractor Maximum Distance from Instructed Target
B
C1
D1
C2
D2
C3
D3
C4
D4
Convergence Angular Demand (°)
10
6
5
10
15
20
Time (Sec)
Block C: Vergence Stimulus with Distractor Minimum Distance from Instructed Target
C
C1
D1
C2
D2
C3
D3
C4
D4
Convergence Angular Demand (°)
10
6
5
10
15
20
Time (Sec)
Block D: Vergence Stimulus with Distractor in-between Instructed Target
D
C1
D1
C2
D2
C3
D3
C4
D4
Convergence Angular Demand (°)
10
6
5
10
15
20
Time (Sec)
Block Presentation Sequence: each letter corresponds a block illustrated above
E
Repeat (x1)
A D C B D B A C B A C D A D B C B D A D C B C A
~9 minutes

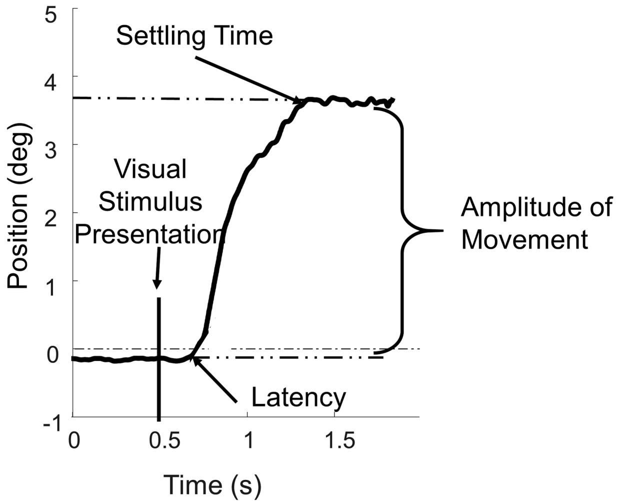


FIG. 3. Vergence eye movement response (black line) showing how latency, settling time, and response amplitude were measured from the eye movement response.

ability to fixate on the same location repeatedly. Accuracy is an assessment of where the average eye movement response is compared to the desired response. The subjects are shown a 4-degree eye movement stimulus. Hence, good accuracy for this study means that, on average, the subject will produce a 4-degree response. However, the subject could make eye movements that are overconverged (say, 5 degrees) or underconverged (say, 3 degrees) and still be accurate if, on average, the response is 4 degrees. Ideally, it is desired that eye movements be accurate (on average, reaching the intended target of 4 degrees) and precise (repeatability of making the same movement).

We hypothesize that healthy control subjects may exhibit motor learning causing the precision and accuracy of the movements to improve as the VET progresses. Control subjects, based upon their symptom surveys, do not report that they fatigue easily. Hence, we hypothesize that their vergence responses may not substantially change during the VET or potentially improve because of motor learning. Conversely, we hypothesize that concussed subjects may exhibit a decrease in vergence precision and accuracy because of the common complaints of being easily distracted and fatigued in their survey symptoms. Both the BPI and the BAI utilize the response amplitude measured from the two distractor-free vergence responses and the six types of vergence responses with visual distractors present.

The BPI is calculated as follows. Variability of the response amplitude of the last four eye movements of each type of movement (distractor-free response, response with a maximum distractor, minimum distractor, and in-between distractor; denoted as Ω in Eq. 1) is calculated for convergence as well as divergence. Variability of the response amplitude is then calculated using the first four eye movements of each movement type (denoted as α in Eq. 1). The ratio of the variability of the response amplitude for the last four responses for each of the four movement types (denoted as C1, C2, C3, and C4 for convergence in Eq. 1 or D1, D2, D3, and D4 for divergence identical to Eq. 1) divided by the variability of the initial four responses for each of the four movement types are computed. There are two ratios calculated: one for the convergence responses and one for the divergence responses. The formula is shown in Equation 1 as the following.

$$\frac{\Omega C1 + \Omega C2 + \Omega C3 + \Omega C4}{\alpha C1 + \alpha C2 + \alpha C3 + \alpha C4} \tag{1}$$

A ratio exactly equal to 1 means there was no variability between the last four and the initial four vergence eye movements. In other words, the vergence responses were stable or consistent throughout the VET. A ratio <1 means the movements showed increased variability toward the end of the vergence endurance test compared to the beginning of the test. A ratio of >1 means an improvement in the precision occurred as the experiment progressed which may occur as the subject becomes better or more familiar with performing the eye movement task. None of the subjects in this study have participated in a previous eye movement experiment; hence, motor learning is possible. The BPI investigates the variability within each movement type from the end of the experiment compared to the beginning of the experiment. The two ratios (one for convergence and then one for divergence) are then summed. A value of 2 means the subject consistently initiated the same response amplitudes throughout the experiment for both convergence and divergence. A value closer to 0 means there was a substantial change in response amplitude at the end of the VET compared to the beginning for both convergence and divergence. A value >2 means that the subject improved in performance.

The BAI is calculated as follows. First, error is defined as the absolute value of the difference between the 4-degree vergence stimulus and the actual response amplitude shown in Equation 2.

$$|4 - Ave\ Response\ Amplitude| \tag{2}$$

In this study, gain is the response amplitude divided by the stimulus amplitude (or 4 degrees) shown in Equation 3.

$$\left|\frac{Average\ Response\ Amplitude}{4}\right| \tag{3}$$

The BAI is assessed by calculating the error and gain of the first four responses at the beginning and the last four movements at the end of the VET. It is computed for convergence and then again for divergence using the distractor-free responses and the three types of vergence responses with distractors. For a subject who is consistent through the experiment, the change in error will be minimal. However, for a subject who may initially be able to initiate the vergence responses but then cannot initiate the responses toward the end of the VET, the error will increase (performance is degrading over time). For a subject who is consistent, the gain will remain constant throughout the experiment. However, for subjects who show a decrease in performance, then the gain will decrease as the experiment progresses. Vergence responses from normal controls are typically within 10% of the intended target.[58] This 10% threshold was also identified with the receiver operator characteristic (ROC) curves.

The normal range for this study was defined to be 10% of the 4-degree vergence stimulus or 0.4 degrees. Hence, changes in errors or changes in gains below 10% where considered normal. Conversely, changes in errors or gains more than 10% where considered abnormal. The change in error and the change in gain were evaluated for each movement type. Hence, there were 16 measurements in total. Each response was quantified as normal (noted as a numerical 0) or abnormal (noted as a numerical 1). The range for the BAI was from 0 to 16. A BAI equal to 0 means the error for the eight movement types and the gains for the eight movement types did not substantially change or were stable as the VET progressed (performance was sustained). A BAI equal to 16 means all the errors for the eight movement types and the gains for the eight movement types substantially changed or showed, on average, a decrease in accuracy as the VET progressed (performance was degraded).

Statistical analysis

The SPSS statistical package was utilized for all statistical calculations (SPSS, Inc., Chicago, IL). Independent-samples *t*-tests were used to compare the control and concussed subjects' group data ($\alpha \leq 0.05$). Normality was assessed before the statistical analysis using Levene's test, which measures equality of variance. The data were normally distributed. An outlier was defined as a measurement greater than 2 standard deviations from the average.[59] At the conclusion of data analysis, subjects were divided into their respective groups of controls and concussed subjects. The following parameters were compared with the independent-samples *t*-tests: peak velocity, response amplitude, latency, and settling time for each of the eight types of movements (two distractor-free responses and six responses with distractors). The BPI, BAI, and percentage of movements of the 192 trials that contained blinks during the transient portion of the response were also compared with an independent-samples *t*-test between the control and concussed groups. Electrophysiology studies support that convergence and divergence are different cells.[60] Further, burst and tonic cells which are assessed by the vergence peak velocity and vergence amplitude, respectively, are also different cells.[61] Statistically, the convergence and divergence peak velocity and final amplitude were treated as independent measures. For the parameters that showed statistically significant differences between groups, an ROC curve was calculated.

ROC curves were calculated for peak velocity and response amplitudes for convergence and divergence distractor-free responses. ROC curves were also computed for the BPI, BAI, and percentage of movements during the experiment with blinks between the latency and settling time. The ideal threshold is identified from the ROC curve by optimizing the best combined true positive rate (TPR) and true negative rate (TNR). The best sensitivity, specificity, and accuracy were calculated for the parameters that were significantly different between the concussed and control groups. The following equations were used to assess sensitivity, specificity, and accuracy where TP is true positive, TN is true negative, FP is false positive, and FN is false negative (Eqs. 4–6):

$$Sensitivity = \frac{TP}{TP + FN} \tag{4}$$

$$Specificity = \frac{TN}{TN + FP} \tag{5}$$

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \tag{6}$$

Results

Ages between the controls and concussed groups were not significantly different ($p > 0.1$). All subjects had a coarse stereopsis of 250 sec of arc, and 17 of the 18 subjects had a visual acuity of 20/20 or better. One control subject's visual acuity was 20/25. Subject symptoms were documented using the PCSS and BIVSS for both the concussed and normal control subjects in Table 1. The average with 1 standard deviation for each group is shown in Table 1. The concussed subjects were significantly different from the control subjects for the PCSS ($t_{(13)} = 4.39$; $p < 0.001$) and the BIVSS ($t_{(13)} = 7.64$; $p < 0.0001$). Concussed subjects were significantly more symptomatic than controls.

An example of a healthy control and a concussed subject's convergence eye movements in response to the distractor-free stimulus are shown in Figure 4. Figure 4 plots the first four (Fig. 4A) and the last four (Fig. 4B) vergence eye movement responses (gray lines) from subject 14, who was a control subject. Convergence is plotted as positive. The dashed line is the stimulus throughout all plots. Figure 4C,D is eye movements from subject 2, who was concussed. The movements from the control subject showed high repeatability (i.e., good precision) and went to the desired stimulus target (i.e., good accuracy). In other words, the instructed target was 4 degrees and the subject consistently produced vergence eye movements with response amplitudes of about 4 degrees at the beginning of the VET (Fig. 4A) and the end of the VET (Fig. 4B). Conversely, the vergence eye movements from the distractor-free stimulus produced by the concussed subject (subject 2) initially were accurate (Fig. 4C). Yet, as the experiment progressed, the last four vergence eye movements from subject 2 have substantially lower response amplitudes (Fig. 4D) showing more error and a decrease in gain (i.e., a decrease in accuracy). In addition, the variability between the responses also increased at the end of the VET compared to the beginning showing a degradation in precision.

Table 1. Vision Symptom Surveys for Control and Concussed Subjects with Average and Standard Deviation (Std.)

	Control subjects scores			*Concussed subjects scores*		
	Subject	*PCSS*	*BIVSS*	*Subject*	*PCSS*	*BIVSS*
	1	0	4	2	12	29
	3	11	6	4	N/A	N/A
	6	N/A	N/A	5	50	50
	7	0	2	8	79	76
	9	10	2	10	28	50
	14	0	2	11	37	40
	15	13	7	12	N/A	N/A
	17	0	0	13	33	32
	18	1	1	16	81	62
Average Std.		4.4	3.0		45.7	48.4
		5.8	2.4		26.0	16.7

BIVSS, Brain Injury Vision Symptom Survey; N/A, not applicable; PCSS, Post-Concussion Symptom Scale.

A similar behavior was observed with divergence responses shown in Figure 5. Figure 5A,B is also from subject 14 (control subject) showing the first and last divergence eye movement responses (gray lines), respectively, in comparison with the distractor-free stimulus shown as a dashed line. Like the results obtained using convergence stimuli, the control subject has good accuracy through the VET because the vergence response amplitude is maintained at approximately 4 degrees throughout the VET. Variability also was similar in the beginning and end. Hence, precision did not substantially change when comparing the responses at the end to those at the beginning of the VET. Conversely, the concussed subject (subject 2) initially can accurately diverge their eyes during the beginning of the VET (Fig. 5C), but by the end of the VET, the last four divergence responses have substantially degraded in performance (Fig. 5D). The response amplitudes of the last four divergence distractor-free responses show substantial increase in error and decrease in gain compared to the initial four responses for the concussed subject. The substantial degradation in performance was observed in 7 of the 9 concussed subjects while the remaining 2 of the concussed subjects showed some decrease in performance. Hence, more degradation in performance was observed in both convergence and divergence eye movements for patients with concussion compared to normal controls.

Average group-level peak velocity and response amplitude for all responses with 1 standard deviation for the control and concussed subjects are shown in Figure 6. The general trend observed is a decrease in both peak velocity and response amplitude for the concussed subjects in comparison to the control subjects across

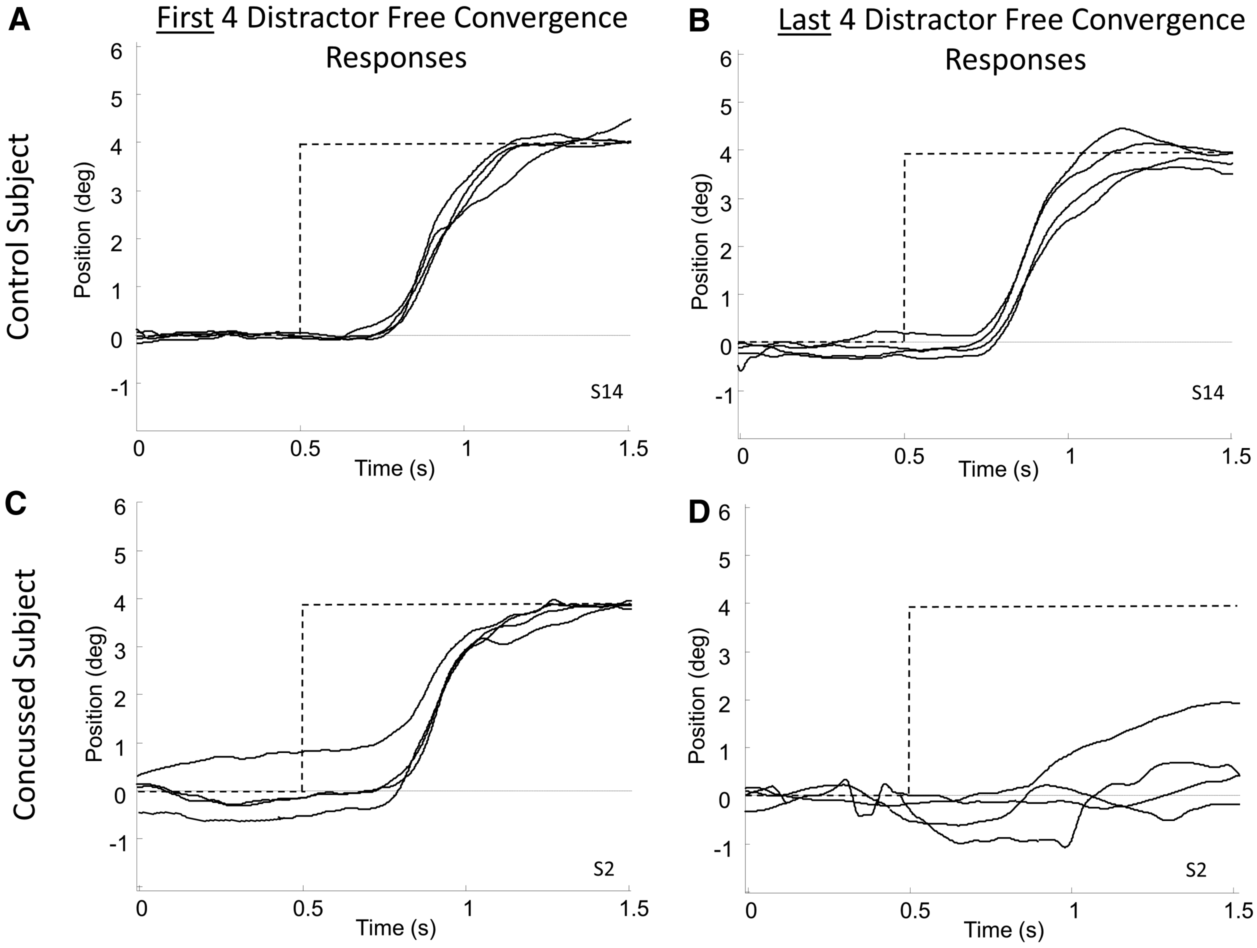


FIG. 4. The first (**A**) and last (**B**) four convergence eye movements (each gray line) from a distractor-free stimulus (dashed lines) from a control subject (S14). The first (**C**) and last (**D**) four convergence eye movements (each gray line) from a distractor-free stimulus (dashed lines) from a concussed subject (S2).

all types of movements. Three parameters measured from the distractor-free responses parameters showed statistical differences in the comparison between control and concussed subjects. The following parameters were significantly different between the groups: 1) convergent peak velocity ($t_{(13)} = 2.49$; $p = 0.027$); 2) divergent peak velocity ($t_{(14)} = 2.19$; $p < 0.05$); and 3) divergent response amplitude ($t_{(16)} = 2.35$; $p = 0.032$). Statistical difference was also observed for peak velocity of the convergent target, which had a distractor at a minimum distance between the control and concussed groups ($t_{(12)} = 2.34$; $p = 0.038$). A detailed analysis of response latency and settling time for all eight movements showed no significant statistical differences between the control and concussed groups ($p > 0.05$).

Figure 7A contains the percentage of trials that contained blinks within the VET during the transient portions (between latency and settling time) of the distractor-free movements. For the control subjects, around 10% of the responses from the VET contained blinks within the transient portion compared to 20% for the concussed subjects. An independent-samples *t*-test showed statistical difference between the percentage of responses with blinks during the VET from the control and concussed subjects ($t_{(14)} = -2.94$; $p = 0.038$). Figure 7B,C shows that the subject average with 1 standard deviation for the BPI and the BAI, respectively. The data show a clear trend differentiating the control and concussed groups for both indices. However, only the BAI showed statistically significant differences between the two groups ($t_{(15)} = -2.13$; $p = 0.05$). The control subjects were more accurate on average compared to the concussed subjects.

The diagnostics odds and ROC curves for five metrics (BAI, BPI, percentage of responses with blinks, response amplitude, and peak velocity) are shown in Figure 8A–E. Table 2 lists the corresponding best sensitivity, specificity, and accuracy of each respective measurement. The best threshold used to differentiate the control and concussed subjects within each metric that produces the highest sensitivity and specificity (identified by the bold circles) were determined through the ROC curve space by identifying the upper-left-most point on the curve. The following thresholds were determined to be optimal from the ROC curves: 1) convergence response amplitude = 2.67 degrees; 2) divergence response amplitude = 2.66 degrees; 3) convergence peak velocity = 19.3 degrees per sec; 4) divergence peak velocity = 12.6 degrees per sec; 5) percentage of responses containing blinks during VET = 15%; 6) BPI = 1.8; and 7) BAI = 7. Subjects who scored higher than the thresholds in the response amplitudes, peak velocities, and BPI would be classified as controls, and subjects who scored at or lower than the thresholds in percent of responses during the VET with blinks and BAI would be classified as controls.

The BAI and divergence response amplitude had the highest accuracy compared to the other measures at 78%. The percentage of responses that contained blinks and convergence

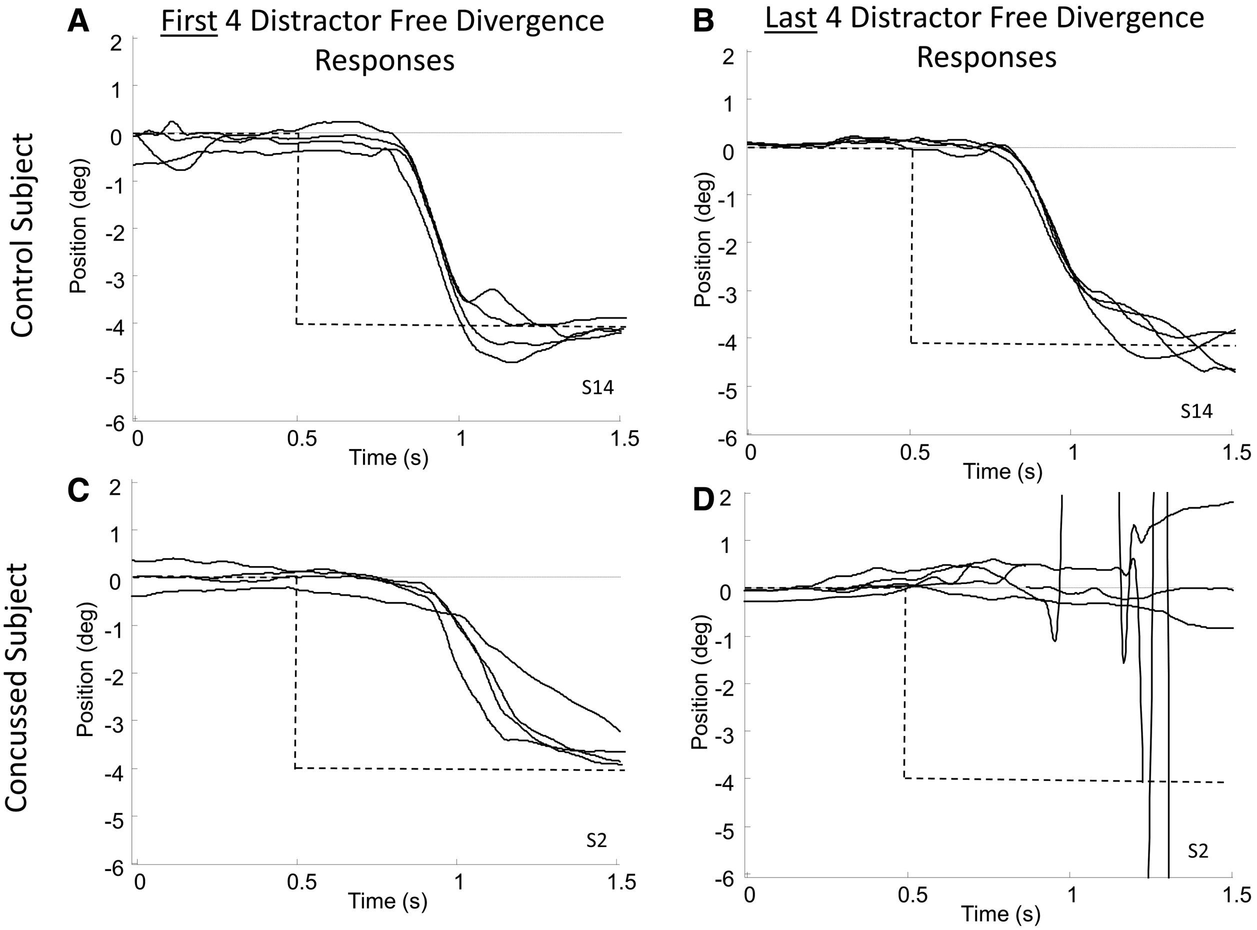


FIG. 5. The first (**A**) and last (**B**) four divergence eye movements (each gray line) from from a distractor-free stimulus (dashed lines) from a control subject (S14). The first (**C**) and last (**D**) four divergence eye movements (each gray line) stimulated from a distractor-free stimulus (dashed lines) from a concussed subject (S2).

response amplitude had an accuracy of 72%. Both peak velocity metrics had an accuracy of 67%, and the BPI had an accuracy of 61%.

Discussion

Accuracy of the Vergence Endurance Test in classifying concussed and control subjects

The results of this study demonstrate that vergence eye movements significantly ($p < 0.05$) degrade over time in concussed subjects compared to healthy controls while participating in the VET. The data indicate that after only an 18-min objective VET, the concussed subjects, but not the control subjects, exhibit decreased response amplitude to the disparity vergence target stimulus. This implies that fatigue decreases vergence eye movement accuracy in those with concussion. Further, the decrease in accuracy suggests that this quantifiable measure of vergence endurance may be used as an indicator for a diagnosis of concussion. As the VET progressed, the concussed subjects' vergence movements deteriorated in terms of accuracy and precision. Additionally, some of the concussed subjects could not maintain fixation (loss of fusion). This loss of fusion could be observed in eye movements. The BAI quantifies the deterioration of vergence accuracy as the VET progresses and has a 78% accuracy in classifying concussed from healthy control subjects. The BAI shows promise as a potential biomarker for concussion.

Percentage of responses that contained blinks within the Vergence Endurance Test

For healthy control subjects, approximately 10% of the responses contained blinks compared to an average of 20% for the concussed group. Blinking is a mechanism which corrects for eye position deviations.[62] More responses containing blinks in the concussed subject group suggests that they may have been struggling to maintain binocular vergence accuracy and precision during the demanding transient portion of testing. Blink rate variability correlates with cognitive performance,[63] and excessive blinking during heavy workloads is commonly reported with brain injury.[64] Brain injury patients are reported to be more fatigued after a 25-min task compared to healthy controls.[65] A review article of many perceptual and cognitive tasks suggests that eye blinks are associated with general fatigue.[57] Perhaps the concussed group within this study exhibited a greater percentage of responses with blinks within the VET because of potential fatigue they may have experienced as the VET progressed.

Vergence peak velocity compared to response amplitude

Several recent studies have suggested that convergence peak velocity is a potential concussion biomarker.[26,66–68] A challenge with vergence peak velocity is that normative data do not exist for the general population. In addition, peak vergence velocity is

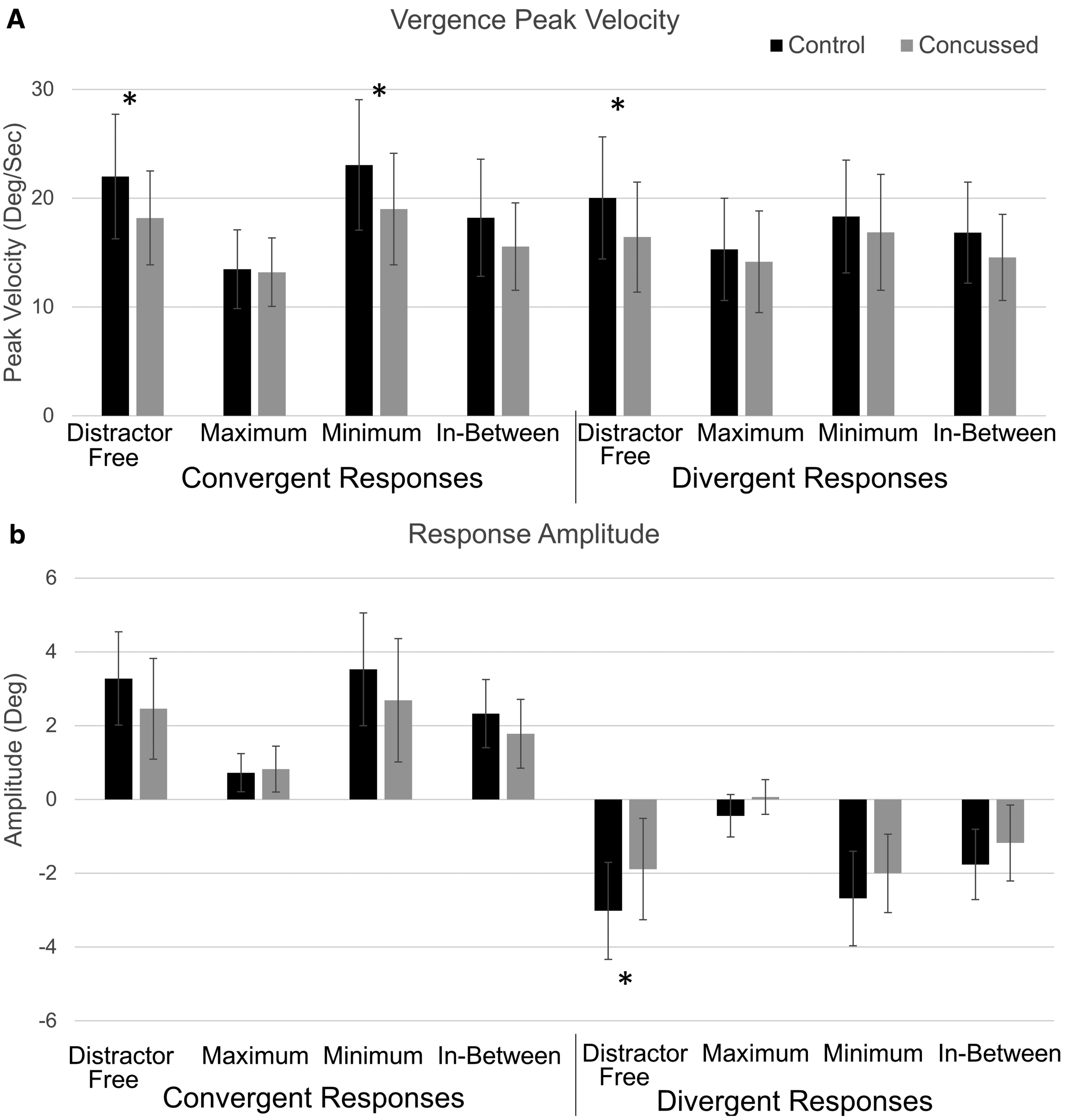


FIG. 6. Group-level analysis of peak velocity (**A**) and response amplitude (**B**) average with 1 standard deviation from control (black bars) and concussed (gray bars) subjects. The asterisks (*) denote statistical difference between control and concussed $p < 0.05$.

variable and has been shown to change as a function of a person's phoria level, the position of the eye that is occluded when the other is fixating on a target.[69–75] For example, when a person is doing more near work such as reading, an esophoric shift of the phoria is observed, which then changes the peak vergence velocity. Hence, caution should be exercised when utilizing vergence peak velocity as a sole biomarker for concussion.

Final response amplitude may be a more robust parameter compared to peak velocity given that normative data are not necessarily needed. When a visual stimulus is given, then the ideal response is to fixate exactly on the instructed visual target. For instance, with this current study, when a 4-degree disparity step vergence stimulus was presented, then the ideal response amplitude would be 4 degrees. This present study also reports how the final response amplitude changes as the VET progresses. To the best of our knowledge, this study is the first to consider the change in vergence response as a function of the test duration as a potential biomarker for concussion. We assessed vergence performance by calculating error and gain to determine the BAI. The BAI is calculated using the response amplitude at the beginning compared to the end of the experiment. One primary result of this current study is during the beginning of the VET, the concussed patients were able to initiate convergence and divergence eye movements. However, as the VET progressed, the concussed subjects' vergence eye movements substantially degraded where the control subjects' vergence eye movements did not.

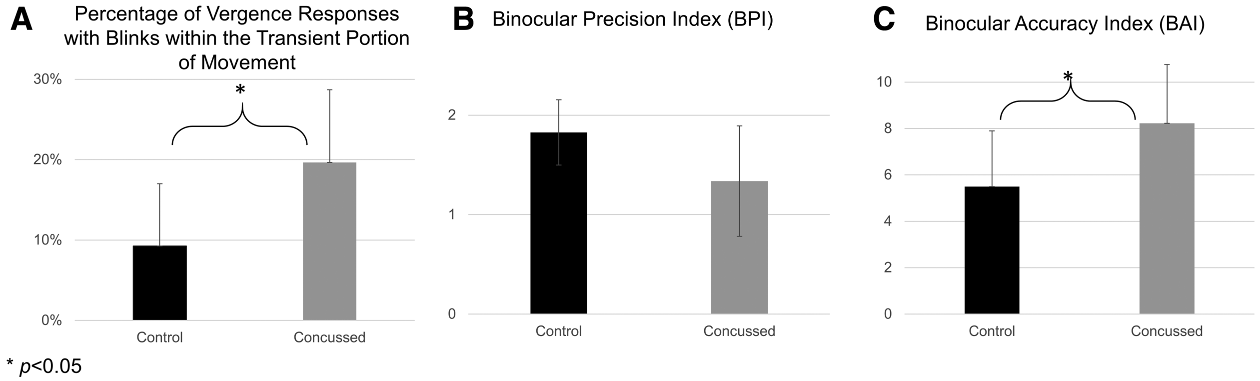


FIG. 7. Bar plots of the mean with 1 standard deviation for control subjects (black bars) and concussed subjects (gray bars) for: (**A**) percentage of blinks observed within the transient portion of the response; (**B**) Binocular Precision Index (BPI); and (**C**) Binocular Accuracy Index (BAI). An asterisk (*) denotes statistical significance $p < 0.05$.

These results support that the degradation of vergence oculomotor function is an independent risk factor to consider when studying concussion. Further, these pilot results suggest that the BAI, which is a measurement of how response amplitude accuracy degrades during the VET, may be a potential quantitative biomarker to assess concussions.

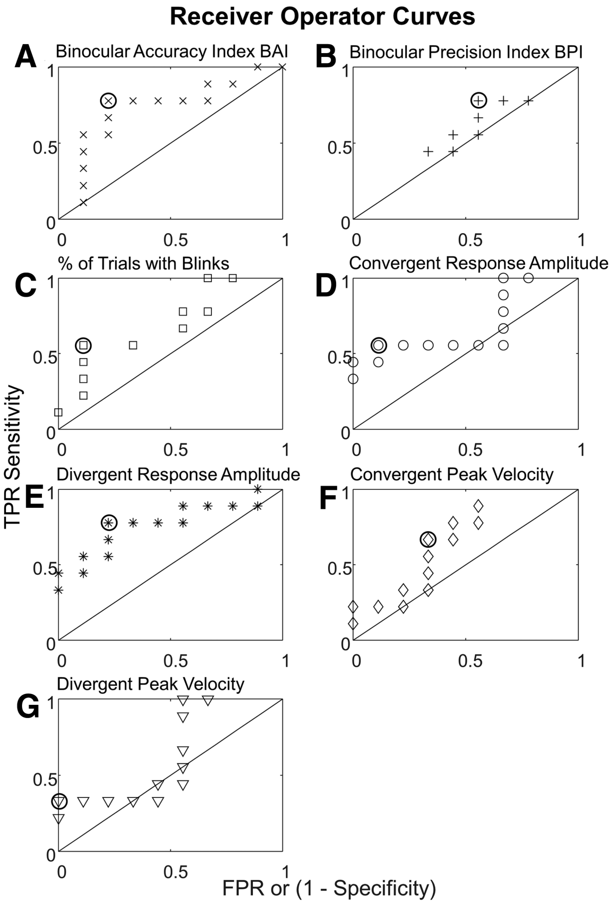


FIG. 8. The receiver operator characteristic (ROC) curves for BAI (**A**), BPI (**B**), percentage of trials that contained blinks during the entire VET (**C**), convergence response amplitude (**D**), divergence response amplitude (**E**), convergence peak velocity (**F**), and divergence peak velocity (**G**). BPI, Binocular Precision Index; FPR, false positive rate; TPR, true positive rate; VET, Vergence Endurance Test.

Refractive correction

The influence of uncorrected refractive error on accommodation and binocular vision is well established.[76,77] All subjects were refracted to best visual acuity with maximum plus. Hence, it was unlikely that variance in refractive error correction was a confounder to the significant results reported in this study.

Comparison to other motor tasks within the literature

Our results show that a decrease in vergence oculomotor performance over time significantly differentiated symptomatic concussed patients from asymptomatic healthy control subjects. Other studies also report significant differences in motor performance in concussed versus healthy control subjects. Servatius and colleagues studied concussed and healthy control subjects and reported no significant differences between groups were observed with the ImPACT test while the U.S. Defense Automated Neurobehavioral Assessment and the Grooved Pegboard Test did reflect significant differences. Servatius and colleagues reported that concussed patients had lower throughput scores for simple reaction time and response inhibition parameters and slower Grooved Pegboard Test performance when using the non-dominant hand compared to controls.[78] Another motor test, the dual-task gait, shows that performance degradation persists post-concussion and is suggested in the monitoring of concussion recovery.[79,80]

Using transcranial magnetic stimulation, research also shows that patients with concussion exhibit slowed fine dexterity

Table 2. Evaluation of Classifiers

Condition	*Sensitivity/ TPR*	*Specificity/ TNR*	*Accuracy*
BPI	78%	44%	61%
BAI	78%	78%	78%
Percentage of responses with blinks	56%	89%	72%
Convergent response amplitude	56%	89%	72%
Divergent response amplitude	78%	78%	78%
Convergent peak velocity	67%	67%	67%
Divergent peak velocity	100%	33%	67%

Percentage rates include sensitivity/true positive rate (TPR), specificity/true negative rate (TNR), and accuracy.

BAI, Binocular Accuracy Index; BPI, Binocular Precision Index.

response times 48 hours post-concussion compared to controls.[81] Vestibular/Ocular Motor Screening is a test that assesses vestibular and saccadic eye movement performance that shows promise in identifying patients who have suffered a concussion.[82,83] Temporal properties as well as anticipatory saccadic eye movements are also significantly different in those with cerebral brain injury compared to controls.[84] Another study suggests that the near point of convergence may be a clinical parameter to consider in the diagnosis of concussion.[80] Significantly reduced peak vergence velocity is also reported in those with concussion compared to controls.[26,69,85] Hence, numerous studies investigating varying aspects of motor, vestibular, saccadic, and vergence performance report a decrease in performance post-concussion compared to healthy controls. This present study shows that the ability to sustain performance is impaired post-concussion. In other words, this is the first study to report that vergence endurance is poor in concussion patients compared to healthy controls.

While several investigations exist studying differences in motor, oculomotor, or vestibular function post-concussion, these studies did not concentrate on how performance may degrade over time within a test. This current study investigates endurance, defined as the change in performance at the beginning of a test compared to the end of a test. This novel finding may be an important independent risk factor to consider in the diagnosis of concussion and evaluation of recovery post-injury.

Potential underlying neural mechanisms

The Dual Mode Theory states that disparity vergence is a two-component system.[86–89] The Fusion Initiating Component (FIC) is preprogrammed and is responsible for moving the eyes toward the new target quickly, but not necessarily accurately. Preprogrammed control is a pre-determined sequence that the brain executes without any additional information from the external environment once the motor sequence is initiated. The Fusion Sustaining Component (FSC) is feedback controlled and is responsible for reducing the error between the intended target and where the eyes are currently located. Feedback control means the brain will compare where the eyes are currently located (sampling the external environment) and where the intended target is. Then, the FSC rotates the eyes so that the difference between the current location of the eyes and the intended target is close to zero. Modeling and signal processing of the FIC shows[40] that it follows the velocity trace signal and is believed to be generated by the ''velocity-encoding'' burst cells described in neurophysiology studies found near the oculomotor nucleus within the midbrain.[61] The FSC mimics the ''position-encoding'' tonic cells, which are distinct cells also within the midbrain.[61] The FIC is assessed by the vergence peak velocity whereas the FSC is assessed by the response amplitude. One potential underlying neural mechanism from this study is the eye movements generated post-concussion suggest dysfunction of the burst and tonic convergence and divergence cells within the midbrain. More investigation is needed to determine whether other neural substrates or the connections between neural substrates are also involved.

Future direction and study limitations

The current study uses a traditional haploscope setting, which requires considerable physical space. The alignment of equipment within a haploscope with the calibration of an eye tracker may present practical challenges when attempting to translate the VET to clinical practice. Efforts are underway to reduce the physical size of the system and complexity of the VET by integrating this metrology into a virtual reality head-mounted display (HMD). This would allow the VET to become portable and hence used at bedside or at a sporting event. Future research will need to compare how the differences in accommodative demand between a haploscope and HMD system impact the results of the VET. Future research will also investigate the optimal amount of time for the VET to maintain high sensitivity and specificity in differentiating concussed compared to healthy control subjects.

While binocular vision is routinely assessed during a primary eye care examination, a more comprehensive assessment of accommodation and binocular vision is not universally performed during a routine clinical examination. Comprehensive assessment of the accommodative and binocular vision systems is usually done as a secondary referral to a binocular vision subspecialty clinic. If we tried to include a table with those optometric results, then there would be many missing data points. It is recommended that future studies include a thorough binocular vision exam with the following measurements: near point of convergence (break and recovery); positive and negative fusional range; vergence facility at near and far; near and far dissociated phoria; amplitude of accommodation; accommodative facility; and stereopsis.

A few of the concussed patients voluntarily reported they experienced physiological diplopia of the intended target toward the end of the VET. Our original protocol did not include a post-questionnaire, but future studies will include a symptom survey immediately pre- and post-VET to assess the visual symptoms a subject is experiencing on the day of the test and what symptoms the VET provokes in subjects.

The techniques developed within this study have the potential to evaluate the effectiveness of different vision therapy/vergence rehabilitation protocols leading to further improvements in oculomotor function and treatments required for recovery post-concussion. More data should be collected to determine whether the trends observed here generalize to a larger population. The methods described here can be deployed within a randomized clinical trial paradigm to assess the differences between control and concussed subjects and how vergence eye movements recorded during the VET may improve after therapeutic interventions or natural recovery. Further, the thresholds identified here for the following metrics (BAI, BPI, percent of responses containing blinks, vergence peak velocity, and response amplitude) may be optimized when studying a larger population.

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Author Disclosure Statement

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