Eye Tracking Results in Postconcussive Syndrome Versus Normative Participants

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Purpose. Standard physical, neurologic, and neuropsychologic examinations may not detect abnormalities after mild traumatic brain injury (mTBI). An analysis of eye movements may be more sensitive to neurologic dysfunction.

Methods. We performed eye tracking assessments in 71 active duty and veteran military personnel with persistent postconcussive symptoms (3 months to 5 years after mTBI) and 75 volunteers with no history of brain injury. Both eyes were sampled at 500 Hz and analyzed for various eye measurement parameters during visual tasks involving the saccadic and smooth systems.

Results. No difference between mTBI and normal participants in main sequence profiles was observed. On the circular task, intersaccadic interval duration was shorter in mTBI compared with normal subjects (horizontal: Cohen's $D = -0.65$; vertical: Cohen's $D = -0.75$). For reading, absolute saccadic amplitudes (Cohen's $D = -0.76$) and average forward saccadic amplitudes were lower (Cohen's $D = -0.61$). Absolute fixation velocity was higher (Cohen's $D = 1.02$), and overall fixation durations (Cohen's $D = 0.58$), regression durations (Cohen's $D = 0.49$), and forward saccadic durations (Cohen's D=0.54) were longer. mTBI participants had more fixations (Cohen's $D = 0.54$) and regressions per line (Cohen's $D = 0.70$) and read fewer lines (Cohen's $D = -0.38$) than normal subjects. On the horizontal ramp task, mTBI participants had lower weighted smooth pursuit gains (Cohen's $D = -0.55$). On the horizontal step task, mTBI participants had shorter mean fixation times (Cohen's $D = -0.55$).

Conclusions. These results suggest vulnerability of the smooth pursuit and saccadic systems in mTBI. Eye tracking shows promise as an objective, sensitive assessment of damage after mTBI. (ClinicalTrials.gov number, NCT01611194, NCT01925963.)

Keywords: brain concussion, eye tracking, postconcussive syndrome, smooth pursuit, saccade

Postconcussive symptoms following mild traumatic brain injury (mTBI) occur in up to 22% of patients following mTBI.[1] The frequency of adverse symptoms following mTBI is also common among military personnel exposed to bomb blasts and explosions during combat.[2] Interventions aimed at improving persistent symptoms following mTBI, such as hyperbaric oxygen (HBO_2), are under investigation,[3] and many others have been tried.[4] An analysis of eye movements offers a potentially sensitive method for detecting the effects of mTBI and investigating the effectiveness of HBO_2 or other potential treatments.

The ability to see clearly requires accurate alignment and control of eyes such that the projected image of an object of interest falls within the fovea area of the retina. In contrast, objects that project beyond the fovea are poorly resolved, lack visual acuity, and possess little or no color information. Eye movements are therefore necessary to position and align the eyes such that the projected image from an object of interest falls upon the fovea, assuring maximum visual acuity and color information. The type of eye movements can be predicted based on the spatial-temporal characteristics of stimulus movement, instructions to the participant, and the positional difference (error) between the location of the fovea and the projected image of the object on the retina. The neurologic control of eye movements involves different functional areas of the brain which are responsible for specific types of voluntary and involuntary eye movements.[5–9] Changes to any of these areas, including their associated neurological pathways, whether by injury, disease, toxins, or even pharmacologic agents, can affect normal eye movement behavior, pupillary control, vergence, and executive function, which is necessary for the planning and execution of eye movements. These changes are both measurable and quantifiable through objective eye tracking recording and analysis.

The fundamental purpose of the oculomotor control system is to first acquire and then stabilize the high-resolution portion of the retina known as the fovea on a target or point of interest, resulting in maximum acquisition of visual information. In this study, we were most interested in two distinct types of eye movements: those involving the saccadic and smooth pursuit systems. Saccades are under voluntary control but can also occur reflexively, are discrete, are most sensitive to position errors, and are noted for their short duration, high velocity, and high acceleration responses. Smooth pursuit eye movements are not under voluntary control, and the proper stimulus must be present to elicit smooth pursuit movement. They are most sensitive to continuously moving objects and have limited velocity-producing capability.

Normal eye movements provide substantial information about brain function, including insight regarding the functional areas and pathways associated with oculomotor control. Significant and different areas of the brain are necessary for coordinated eye movement and visual interpretation. Therefore, eye movement analysis should be sensitive in brain pathologic conditions. For example, eye movement differences between patients with Parkinson's disease and age-matched controls while performing simple visual tracking tasks and while reading have been demonstrated.[10–12] Similarly subtle but distinguishing differences between the eye movements of patients with Parkinson's disease and patients with essential tremor have been documented.[13,14]

To characterize the effects of mTBI on eye movement, visually based activities involving tracking, reading, and memory have been investigated with the intent to identify the tasks and eye measurement variables most sensitive to mTBI. In one study,[15] the eye movements of individuals diagnosed with mTBI and 26 control participants without TBI were measured at 500 Hz from a two-dimensional eye tracking system. Participants tracked targets in the horizontal and vertical directions and performed various tracking tasks. Eye position data were analyzed through visual inspection. The investigators used automated analysis algorithms to determine response latency, velocity gain, number of saccades, saccadic amplitude, duration, velocity, acceleration, and fixation stability. In that study, the mTBI data of 60 participants symptomatic of mTBI were statistically analyzed and compared with an identically tested small control group of 26 asymptomatic volunteers.[15] Significant differences for several tasks and eye movement parameters were found, suggesting that the associated regions of the brain are sensitive to injuries due to mTBI. These results were based on limited samples and, to date, have not been verified independently.

The present studies, the Brain Injury and Mechanisms of Action of Hyperbaric Oxygen (HBO_2) for Persistent Post-Concussive Symptoms after mTBI (BIMA) and a parallel noninterventional study in healthy volunteers with no history of brain injury, Development of Normative Datasets for Assessments Planned for Use in Patients with Mild Traumatic Brain Injury (Normal), have a larger sample size and a well-balanced proportion of participants in each group that makes the two groups more comparable. The results reported herein investigate potential performance differences between the mTBI and normal populations enrolled in the BIMA and Normal studies with the aim of identifying which visual tasks and measurement parameters are most sensitive in patients with symptoms following mTBI.

Methods

Study Design

Eye tracking assessments were completed by trained technicians in a central outcomes assessment facility as part of two companion studies: an exploratory, randomized, double-blind interventional study in active duty and veteran military personnel with persistent postconcussive symptoms after mTBI (BIMA)[16] and a parallel noninterventional study in healthy volunteers with no history of brain injury (Normal) (Weaver LK, et al., manuscript submitted, 2018). Participants in the Normal study completed nearly the same outcome assessments on the same schedule, with the same evaluators, using the same equipment as in BIMA. The purpose of BIMA was to determine whether hyperbaric oxygen improved outcomes compared with sham and identify outcome assessments for potential future efficacy trials. The Normal study allowed the investigators to explore which assessments were sensitive in the mTBI population and how assessment performance might be expected to change over time.

BIMA participants were recruited from Evans Army Community Hospital in Fort Carson, Colorado, Madigan Army Medical Center at Joint Base Lewis McChord, Washington, and Naval Hospital Camp Lejeune, North Carolina. Eye tracker assessments were conducted at an Outcomes Assessment Center (OAC) in Colorado Springs, Colorado, United States. Eligibility criteria for the BIMA study included active duty or veteran participants ages 18 to 65 years with persistent symptoms from a mTBI that occurred on active duty 3 months to 5 years prior to baseline screening; was caused by nonpenetrating trauma or blast exposure; and resulted in a period of loss of, or a decreased level of, consciousness (up to 30 minutes), a loss of memory for events immediately before or after the injury (up to 24 hours), or alteration in mental state at the time of the injury (becoming dazed or confused). Exclusion criteria included individuals with contraindications to hyperbaric pressurization and HBO_2, conditions that might confound outcome measures such as refractive eye surgery within 90 days prior to enrollment, or life experiences that might expose study blinding. Additional details regarding BIMA study design can be found elsewhere.[16]

Participants in the noninterventional Normal study were recruited from the Colorado Springs area, and all assessments were performed at Evans and the OAC. Enrollment was divided into subgroups based on age and sex with 63 male participants between the ages of 18 and 65 years and 20 women ages 18 to 35 years. Exclusion criteria included the following: known history of brain injury; diagnosis of neurologic disorders; active therapy for affective, behavioral, or psychologic disorders; diabetes, chronic migraines; headaches, or dizziness; history of combat; post-traumatic stress disorder (PTSD); prescription drug use known to impact neurologic function; atrial septal defects; developmental delays; habitual use of cannabis or history of illicit drug or alcohol abuse; binocular vision not correctable to 20/50; deafness; and active malignancy. Performance on eye tracking tasks was not an exclusion criterion. Both the BIMA and Normal studies received approval from the US Army Medical Research and Materiel Command Institutional Review Board. Participants offered written consent and received stipends for participation if participation occurred off duty. The investigator(s) adhered to the policies regarding the protection of human subjects as prescribed by Code of Federal Regulations (CFR) Title 45, Volume 1, Part 46; Title 32, Chapter 1, Part 219; and Title 21, Chapter 1, Part 50 (Protection of Human Subjects), and all procedures were conducted in compliance with the tenets of the Declaration of Helsinki.

Eye Tracking

During the eye tracking assessment, the horizontal and vertical positions of each eye were simultaneously recorded at 500 Hz with an EyeLink 1000 (SR Research, Ottawa, Ontario, Canada) remote eye tracking system set up for pupil-corneal tracking. The EyeLink 1000 was calibrated using the built-in, nine-point, two-dimensional calibration procedure. This procedure was performed with each participant prior to actual data collection to establish the relationship, repeatability, and accuracy between a calibration target point and actual eye position. Calibration involved asking participants to fixate on nine separate points that were mapped to the dimensions of the display that established the relationship between screen pixel coordinates and eye position. To minimize head movement during calibration and during the visual tracking and reading tasks, the head was stabilized with an adjustable head and chin rest (SR Research). Visual tracking tasks and reading stimuli were created using Experimental Builder (SR Research). All stimuli were displayed on a 24-inch diagonal, 1920 H by 1200 V pixel resolution LCD monitor. The monitor was vertically refreshed at a rate of 120 Hz and was positioned 75 cm from the participant's eyes, resulting in a visual target area of ±19° H by ±13° V. Testing was performed at baseline, 13 weeks, and 6 months after enrollment in both studies. Baseline results are reported herein.

Visual Tasks

The right and left eye movements of each participant were recorded while they performed a variety of tracking tasks, including reading and tasks involving memory and antisaccadic or antidirectional responses. Tasks were developed to elicit conjugate eye movement responses from both the saccadic and smooth pursuit systems, which were presented along the horizontal and vertical tracking directions. Performance measures reported for each task represent traditional domains and are listed below.

Based on the work of Munoz et al.[7] and others,[17–20] the following tasks were selected:

- 2-Point (saccadic): Two static reference points were presented, separated by ±10 degrees. The participant was asked to voluntarily move his or her gaze as quickly as possible between these two static points. Total estimated time: 10 seconds. Performance measures: saccadic amplitude, duration, velocity and acceleration; fixation time and velocity.
- Circular (smooth pursuit): The target moved in a circular pattern, and the participant was instructed to follow the pattern as closely as possible. Rotational period 0.25 seconds (0.4 Hz), amplitude ±9°, peak velocity 22°/s. Total estimated time: 34 seconds. Performance measures: saccadic amplitude, intersaccadic interval duration, and velocity.
- Horizontal and vertical ramp (smooth pursuit): Target motion consisted of multiple random segments of different velocities, durations and directions (horizontal direction for the horizontal ramp task and vertical direction for the vertical ramp task). Performance measures: saccadic amplitude, intersaccadic interval duration, weighted intersaccadic interval velocity; weighted smooth pursuit gains.
  - Horizontal: Maximum velocity 16.72°/s, minimum 4.20°/s, weighted average velocity 9.07°/s, mean duration 1.082 ± 0.536 seconds, maximum duration 2.576 seconds, minimum 0.554 seconds. Total estimated time: 30 seconds.
  - Vertical: Maximum velocity 14.45°/s, minimum 3.60°/s, weighted average velocity 7.08°/s, mean duration 1.082 ± 0.536 seconds, maximum duration 2.576 seconds, minimum 0.554 seconds. Total estimated time: 30 seconds.
- Horizontal and vertical step (saccadic): The target jumped laterally or horizontally (or vertically for vertical step), target was presented as a gap target where the first stimulus disappeared and then the second was presented. It was randomized for time and position of the jump. Performance measures: saccadic amplitude, duration, velocity and acceleration; fixation time and velocity.
  - Horizontal: Mean step size 12.10° ± 8.63°, minimum step size 0.94°, maximum 29°, mean position duration 1.16 ± 0.48 seconds, minimum duration 0.616 seconds, maximum 2.086 seconds. Total estimated time: 30 seconds.
  - Vertical: Mean step size 7.28° ± 5.13°, minimum step size 0.61°, maximum 17.26°, mean position duration 1.16 ± 0.48 seconds, minimum duration 0.616 seconds, maximum 2.086 seconds. Total estimated time: 30 seconds.
- Reading (saccadic): Five texts with 10 lines of text each were presented. Reading difficulty ranged from elementary to 12th grade.[17] The participant was asked to read each text at their own pace and to close their eyes after each text was read.[18] Total estimated time: self-paced. Performance measures: forward and regressive saccadic amplitude, primary return sweep amplitude, forward fixation and regression duration, lines read, fixation and regressions per line.
- Memory guided on and off (saccadic): Two types of trials were included. For the first, the participant was shown a pattern of positions that remained illuminated, and the participant followed the pattern with his or her gaze. For the second trial, the pattern was shown and then disappeared, and the participant tried to repeat the pattern.[19] Target positions 0°, ±5°, and ±10°, duration 1.5 second per target position. Total estimated time: 60 seconds each. Performance measures: Target off and target on hits and misses.
- Antisaccade (saccadic): The participant was instructed to move eyes in an equal but opposite direction from the actual target position.[20] Target positions ±2°, ±7°, ±9°, ±12°, and ±17°, duration at each target position 1.7 seconds. Total estimated time: 33 seconds. Performance measures: hits and misses.

Random pursuit and horizontal sinusoidal tasks were also measured and will be the subject of another manuscript.

Reading, antisaccade, and memory-guided tasks were always given in the same order, whereas the remaining subassessments were presented in a randomized order to account for the effects of participant fatigue. The randomized sequence of the remaining subtests remained the same for a single participant across visits. Performance on each subassessment was recorded for right and left eye, and for each eye the subassessment was performed in the vertical and horizontal directions. A collection of outcome metrics was produced for each assessment, and measures representing saccades, fixation, and intersaccadic intervals are reported along with weighted gains for horizontal and vertical ramp tasks.

Data Processing Methods

Eye movement recording data from each participant were extracted by a computer program developed by the first author (PAW) that converts pixel coordinates to eye position angles into individual files for eye (right or left), direction (horizontal or vertical), and associated stimulus positions. In addition, files were created that identified the locations of blinks and other artifacts. Investigators, trained in ocular motor responses and eye movement behaviors, visually inspected and commented on these files prior to automated analysis. To assure analysis accuracy, the analyzed data were compared manually with the visual recordings. Sections of data that included blinks and/or non–blink-related artifact were excluded from automated analysis.

From the position data, a two-point central difference method originally described by Bahill et al.[21] was used to compute the velocities and accelerations for each eye in both the horizontal and vertical directions. Saccades are identified in the program by using velocity and acceleration thresholds of $>20°/s$ and $>400°/s^2$, respectively, for saccadic tasks and $>30°/s$ and $>2000°/s^2$ for smooth pursuit tasks, along with sustained eye movement in the same direction and appropriate duration. Saccades less than 0.1° were identified but not counted. The maximum or peak velocity and peak accelerations were determined during the saccadic trajectory. Saccadic amplitude was determined based on the positional differences between the start and end positions of the saccade. The two-point difference method was effective at measuring saccadic corrections during periods of smooth pursuit. During fixation and smooth pursuit, the duration and velocity of the eye was determined. Weighted smooth pursuit gain was determined based on Equation 1 during the intersaccadic interval. During calculation, the target velocity used to analyze gain was continued past the presented target velocity until the subject made a corrective saccade in the direction of the new target direction or velocity. A gain of 1 occurs when both the eye and target are moving at the same speed. Gains greater than 1 occur when the eye is moving faster than the target. Gains less than 1 correspond to the case where the eye is moving slower than the target. Gains less than 1 suggest poorer tracking and likely included more corrective saccades.

$$G_w = \sum \frac{\left(\sum_{i=1}^{n} t_i\right) * \frac{\bar{v}}{v_s}}{t_{tot}} \tag{1}$$

where G_w is the total weighted gain, t_i is the intersaccadic pursuit time, $\bar{v}$ is the average velocity of smooth pursuit within each segment, v_s is the segment velocity, and t_{tot} is the total task time.

Statistical Methods

Results for a given parameter were averaged for the participant by dividing by the total measurements made for that participant for that task. For example, the total of all fixation velocities measured for a participant during a task was divided by the number of fixations observed during that task. The independent two-sample *t*-test was used to test for significance between BIMA and Normal population outcomes. Potential covariates were tested using general linear models to identify whether the sex differences between the BIMA and Normal study populations were a potential explanatory variable for any of the tasks, as well as the potential influence of number of injuries (1 vs. >1), age (continuous), time since injury (<1 vs. >1 year), and PTSD. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses. Given the exploratory nature of the studies, unadjusted *P* values are presented, and *P* values adjusted for multiple comparisons using the Holm-Bonferroni procedure are provided.[22] Consistency of the size and direction of observed effects are evaluated using Cohen's *D*. High correlations between right and left eyes were observed, and results for the right eye are presented.

Results

The characteristics of the BIMA and Normal populations are provided in Table 1. The median age of the 71 randomized BIMA participants was 32 years (range, 21 to 53 years), 99% male, and 82% Caucasian, and the majority (82%) had some college education. Other characteristics of the BIMA population included 96% active duty, 49% with comorbid diagnosed PTSD, and 28% with most recent qualifying injury 3 months to 1 year prior to enrollment. The mean number of mTBIs prior to enrollment was 3.6 (range, 1 to 18). Thirty-two percent reported only blast injuries in their lifetime (as opposed to blunt force trauma). Eighty-three participants were enrolled in the Normal study; 75 met all inclusion criteria and completed required study visits. In contrast to BIMA, 77% of the Normal population were men and were on average 6 years older than the BIMA population. The study populations were otherwise comparable in terms of race, ethnicity, and education.

Table 2 provides the number of participants available for each task analysis. At least one baseline eye tracking assessment result was available for 62 BIMA and 63 Normal participants (125 total), with 9 (12.6%) of 71 randomized BIMA participants and 12 (16%) of 75 Normal participants without eye tracker data due to the participant's inability to successfully complete the calibration procedure. For example, those with gaze abnormalities would have more difficulty calibrating. Some participants were able to complete some but not all tasks, which can result from fatigue and difficulty focusing on tasks. Results from participants on individual tasks were excluded if the quality on that particular task was inadequate. Results from 19 of 75 participants (25%) in the Normal group were not considered normal for all tasks based on visual inspection of the recorded eye data by the subject matter expert (PAW) for this testing procedure. These data remained as part of the normal comparator group.

Table 3 provides a summary of the average number of measurements of a parameter, the mean values by study,

Table 1. Participant Characteristics

	Normal ($n = 75$)	BIMA ($n = 71$)
Male, *n* (%)	58 (77%)	70 (99%)
Age (y)		
Mean (SD)	39 (13)	33 (7)
Median (min–max)	38 (18–65)	32 (21–53)
Education, *n* (%)		
High school or less	6 (8%)	13 (18%)
Some college or more	69 (92%)	58 (82%)
Race, *n* (%)		
White or Caucasian	62 (83%)	58 (82%)
Other	13 (17%)	13 (18%)
Ethnicity, *n* (%)		
Not specified	1 (1%)	0
Hispanic or Latino	7 (9%)	13 (18%)
Not Hispanic or Latino	67 (89%)	58 (82%)

Table 2. Number of Available Participants by Task and Study

Task	Number of BIMA Participants	Number of Normal Participants
Antisaccadic	59	63
Circular	59	61
Horizontal step	61	62
Vertical step	62	63
Horizontal ramp	60	59
Vertical ramp	52	56
Reading	54	63
Memory-guided on	59	63
Memory-guided off	60	63
Two point	61	63

Table 3. Comparison of Parameter Estimates for Seven Tasks Between BIMA and Normative Participants Right Eye Measures at Baseline

		Number of Observations		Standard Scores				
Eye Tracker Test	Parameter	BIMA, Mean (SD)	Normal, Mean (SD)	BIMA, Mean (SD)	Normal, Mean (SD)	Cohen's *D*	Unadjusted *P* Value	Adjusted *P* Value
Two-point ($N = 124$)	Absolute saccadic amplitude (°)	34.57 (6.49)	35.86 (7.35)	10.63 (2.51)	11.07 (2.72)	−0.17	0.35	0.35
	Saccadic duration (ms)	34.57 (6.49)	35.86 (7.35)	47.77 (11.24)	44.67 (9.94)	0.29	0.11	0.32
	Absolute peak velocity (°/s)	34.57 (6.49)	35.86 (7.35)	303.11 (65.40)	329.82 (79.30)	−0.37	0.04	0.17
	Absolute peak acceleration (°/s^2)	34.57 (6.49)	35.86 (7.35)	17138 (4078.9)	18934 (4640.7)	−0.41	0.02	0.12
	Mean fixation time (ms)	34.57 (6.49)	35.86 (7.35)	178.66 (66.31)	194.68 (64.33)	−0.25	0.17	0.35
	Absolute fixation velocity (°/s)	34.57 (6.49)	35.86 (7.35)	2.80 (1.06)	2.40 (0.63)	0.46	0.01	0.07
Circular ($N = 120$)	Absolute saccadic amplitude (°), H	81.46 (23.37)	68.51 (17.01)	1.73 (0.45)	1.55 (0.35)	0.45	0.02	0.06
	Absolute saccadic amplitude (°), V	77.27 (15.80)	67.15 (19.65)	2.26 (0.64)	2.02 (0.59)	0.39	0.03	0.06
	Inter saccadic interval duration (ms), H	81.46 (23.37)	68.51 (17.01)	364.93 (114.55)	444.21 (129.18)	−0.65	<0.01	<0.01
	Inter saccadic interval duration (ms), V	77.27 (15.80)	67.15 (19.65)	367.16 (88.54)	476.07 (185.51)	−0.75	<0.01	<0.01
	Absolute intersaccadic interval velocity (°/s), H	81.46 (23.37)	68.51 (17.01)	12.39 (1.49)	12.99 (1.19)	−0.44	0.02	0.06
	Absolute intersaccadic interval velocity (°/s), V	77.27 (15.80)	67.15 (19.65)	11.39 (1.62)	12.11 (2.01)	−0.40	0.03	0.06
Horizontal ramp ($N = 119$)	Absolute saccadic amplitude (°)	96.40 (23.08)	89.25 (16.28)	1.58 (0.35)	1.52 (0.21)	0.19	0.30	0.30
	Inter saccadic interval duration (ms)	96.40 (23.08)	89.25 (16.28)	273.16 (69.82)	297.00 (62.41)	−0.36	0.05	0.10
	Weighted abs. intersaccadic interval velocity (°/s)	27.00 (0.00)	27.00 (0.00)	5.33 (1.41)	5.97 (0.91)	−0.55	<0.01	0.01
	Smooth pursuit gain weighted	27.00 (0.00)	27.00 (0.00)	0.59 (0.15)	0.66 (0.10)	−0.55	<0.01	0.01
Horizontal step ($N = 123$)	Absolute saccadic amplitude (°)	69.38 (18.68)	62.02 (18.60)	4.79 (1.17)	5.22 (1.18)	−0.37	0.04	0.13
	Saccadic duration (ms)	69.38 (18.68)	62.02 (18.60)	33.40 (6.44)	31.66 (3.98)	0.33	0.07	0.15
	Absolute peak velocity (°/s)	69.38 (18.68)	62.02 (18.60)	182.76 (53.60)	205.19 (47.41)	−0.44	0.02	0.06
	Absolute peak acceleration (°/s^2)	69.38 (18.68)	62.02 (18.60)	10598 (3263.8)	12062 (2998.4)	−0.47	0.01	0.05
	Mean fixation time (ms)	69.38 (18.68)	62.02 (18.60)	350.29 (124.20)	415.74 (115.09)	−0.55	<0.01	0.02
	Absolute fixation velocity (°/s)	69.38 (18.68)	62.02 (18.60)	2.39 (0.93)	2.28 (0.74)	0.13	0.46	0.46
Reading ($N = 117$)	Absolute saccadic amplitude (°)	472.41 (151.32)	436.49 (114.59)	3.87 (0.65)	4.42 (0.79)	−0.76	<0.01	<0.01
	Absolute fixation velocity (°/s)	472.41 (151.32)	436.49 (114.59)	2.48 (0.49)	2.01 (0.42)	1.02	<0.01	<0.01
	Regression saccadic amplitude (°)	123.44 (55.32)	99.11 (49.55)	−1.79 (0.31)	−1.87 (0.39)	0.25	0.18	0.37
	Average forward saccadic amplitude (°)	305.57 (97.62)	289.63 (72.07)	2.92 (0.55)	3.30 (0.66)	−0.61	<0.01	<0.01
	Primary return sweep amplitude (°)	43.39 (10.97)	47.75 (8.15)	−15.58 (1.06)	−15.63 (1.11)	0.05	0.80	0.80
	Overall fixation duration (ms)	472.41 (151.32)	436.49 (114.59)	243.88 (42.86)	222.28 (30.93)	0.58	<0.01	0.02
	Regression duration (ms)	166.48 (62.09)	146.60 (53.34)	258.48 (53.92)	232.48 (52.11)	0.49	<0.01	0.03
	Forward saccadic duration (ms)	305.52 (97.67)	289.60 (72.09)	237.57 (43.91)	217.87 (27.85)	0.54	<0.01	0.02
Vertical ramp ($N = 108$)	Absolute saccadic amplitude (°)	74.98 (14.05)	72.96 (13.84)	1.67 (0.47)	1.49 (0.24)	0.47	0.02	0.08
	Inter saccadic interval duration (ms)	74.98 (14.05)	72.96 (13.84)	328.40 (75.72)	355.29 (87.67)	−0.33	0.09	0.27
	Weighted abs.intersaccadic interval velocity (°/s)	26.00 (0.00)	26.00 (0.00)	2.96 (0.63)	3.11 (0.92)	−0.19	0.31	0.63
	Smooth pursuit gain weighted	26.00 (0.00)	26.00 (0.00)	0.42 (0.09)	0.44 (0.13)	−0.19	0.31	0.63
Vertical step ($N = 125$)	Absolute saccadic amplitude (°)	63.79 (18.56)	55.98 (13.94)	3.12 (0.75)	3.48 (0.77)	−0.47	<0.01	0.05
	Saccadic duration (ms)	63.79 (18.56)	55.98 (13.94)	31.57 (4.27)	31.28 (4.53)	0.07	0.71	0.71
	Absolute peak velocity (°/s)	63.79 (18.56)	55.98 (13.94)	142.53 (36.60)	156.46 (37.14)	−0.38	0.04	0.11
	Absolute peak acceleration (°/s^2)	63.79 (18.56)	55.98 (13.94)	8194.5 (2207.8)	9031.6 (2278.1)	−0.37	0.04	0.11
	Mean fixation time (ms)	63.79 (18.56)	55.98 (13.94)	371.22 (121.93)	436.68 (117.10)	−0.55	<0.01	0.02
	Absolute fixation velocity (°/s)	63.79 (18.56)	55.98 (13.94)	3.52 (1.05)	3.05 (0.95)	0.46	0.01	0.05

H, horizontal direction; V, vertical direction.

TABLE 4. Comparison Between BIMA and Normal Participants in Three Tasks at Baseline for the Right Eye*

Eye Tracker Test	Parameter	BIMA, Mean (SD)	Normal, Mean (SD)	Cohen's *D*	Unadjusted *P* Value	Adjusted *P* Value
Antidaccadic ($N = 122$)	Hits	6.71 (2.51)	7.49 (1.92)	−0.35	0.06	0.12
Antidaccadic	Misses	3.29 (2.51)	2.51 (1.92)	0.35	0.06	0.12
Memory-guided off ($N = 123$)	Targets off hits	9.37 (1.65)	9.68 (1.23)	−0.22	0.23	0.46
Memory-guided off	Targets off misses	0.63 (1.65)	0.32 (1.23)	0.22	0.23	0.46
Memory-guided on ($N = 122$)	Targets on hits	9.27 (1.51)	9.87 (0.42)	−0.54	<0.01	<0.01
Memory-guided on	Targets on misses	0.73 (1.51)	0.13 (0.42)	0.54	<0.01	<0.01
Reading ($N = 117$)	Lines read	44.28 (10.00)	47.81 (8.26)	−0.38	0.04	0.04
Reading	Fixations per line	6.92 (1.69)	6.09 (1.39)	0.54	<0.01	<0.01
Reading	Regressions per line	3.75 (1.04)	3.05 (0.94)	0.70	<0.01	<0.01

* Hits and misses reported for left eye.

Cohen's *D*, and adjusted and unadjusted *P* values comparing the outcomes between the BIMA and Normal populations for each task and parameter. A comparison of the main sequence profiles between the BIMA and Normal groups revealed no obvious differences (data not shown). During smooth pursuit tasks, BIMA participants made nominally significantly larger saccades compared with Normal participants during the circular task (1.73° ± 0.45° vs. 1.55° ± 0.35°; Cohen's $D =$ 0.45) and observably larger, but not significantly, for horizontal and vertical ramp tasks. BIMA participants made smaller amplitude saccades for each of the saccadic tasks with only the vertical step task significant after multiplicity adjustment (vertical step: 3.12° ± 0.75° vs. 3.48° ± 0.77°; Cohen's *D* =0.47). Consistently, peak saccadic velocity and acceleration were lower for all saccadic tasks with nominally significant differences between BIMA and Normal participants observed for the horizontal step task (absolute peak saccadic velocity: 182.76°/s ± 53.60°/s vs. 205.19°/s ± 47.41°/s; Cohen's $D =$ –0.44; absolute peak saccadic acceleration: 10,598°/s^2 ± 3263°/s^2 vs. 12,062°/s^2 ± 2998°/s^2; Cohen's $D = –0.47$). Mean intersaccadic interval duration for smooth pursuit tasks and mean fixation time for saccadic tasks were lower in BIMA participants compared with Normal with significant differences observed for the intersaccadic interval durations for the circular task (horizontal: 364.93 ms ± 114.55 ms vs. 444.21 ms ± 129.18 ms; Cohen's $D = –0.65$; vertical: 367.16 ms ± 88.54 ms vs. 476.07 ms ± 185.51 ms; Cohen's $D = –0.75$) and mean fixation time for the horizontal (350.29 ms ± 124.20 ms vs. 415.74 ms ± 115.09 ms; Cohen's $D = –0.55$) and vertical step (371.22 ms ± 121.93 ms vs. 436.68 ms ± 117.10 ms; Cohen's $D = –0.55$) tasks. Intersaccadic interval velocity was significantly lower for the circular (horizontal: 12.39°/s ± 1.49°/s vs. 12.99°/s ± 1.19°/s; Cohen's $D = –0.44$) and horizontal ramp (5.33°/s ± 1.41°/s vs. 5.97°/s ± 0.91°/s; Cohen's $D = –0.55$) tasks. The weighted smooth pursuit gains for horizontal ramp were lower for the BIMA group compared with the Normal group (0.59 ± 0.15 vs. 0.66 ± 0.10; Cohen's $D = –0.55$). Absolute fixation velocities were higher for BIMA participants compared with Normal participants for the vertical step task (3.52°/s ± 1.05°/s vs. 3.05°/s ± 0.95°/s; Cohen's $D = 0.46$).

For reading, absolute saccadic amplitudes (Cohen's $D =$ –0.76) and average forward saccadic amplitudes were lower (Cohen's $D = –0.61$). Absolute fixation velocity was higher (Cohen's $D = 1.02$) and overall fixation durations (Cohen's $D =$ 0.58), regression durations (Cohen's $D = 0.49$), and forward saccadic durations (Cohen's $D = 0.54$) were longer. Table 4 shows that BIMA participants read fewer lines (44.28 ± 10.00 vs. 47.81 ± 8.26 lines; Cohen's $D = –0.38$) and had statistically significantly more fixations per line (6.92 ± 1.69 vs. 6.09 ± 1.39; Cohen's $D = 0.54$) and regressions per line (3.75 ± 1.04 vs. 3.05 ± 0.94; Cohen's $D = 0.70$) than did Normal participants.

Table 4 also provides results for hits and misses for the antisaccadic task and the memory-guided task, as well as performance on the reading task. There were significantly more misses (0.73 ± 1.51 vs. 0.13 ± 0.42; Cohen's $D = 0.54$) recorded for the memory-guided on task for BIMA participants compared with Normal participants. The memory-guided off task and the antisaccadic task had consistent but not statistically significant results.

Figures 1a–1c provide a characteristic example of the performance of a BIMA and Normal participant on the circular task where BIMA participants had higher saccadic amplitudes, shorter intersaccadic interval durations, and higher intersaccadic interval velocities compared with Normal participants. Figures 2a and 2b show a characteristic example of the performance of a BIMA participant and a Normal participant on the reading task. On this task, BIMA participants had lower saccadic amplitudes, longer fixation durations, regression durations, and forward saccadic durations, as well as more fixations and regressions per line, resulting in fewer lines read overall.

DISCUSSION

Eye tracking provides a unique, assessment of eye movements independent of patient self-reports that can be helpful diagnosing adverse brain-related sequelae after brain injury. In addition, eye tracking tests can be useful to track progress or effects of therapy after brain injury. A variety of visual stimuli can be selected to investigate different areas of brain function and associated neurologic pathways. Many of the outcome measures produced by the eye tracker protocol we used were likely affected by brain injury due to mTBI. Our findings support previous research indicating that there are differences in eye movement between normative individuals and those with problems following mTBI.[15,23]

The effect of persistent symptoms following mTBI on eye movement response and oculomotor control is impactful and wide ranging. In our study, after adjustments for multiple comparisons, we found statistically significant differences between Normal participants and those with symptoms following mTBI for many visual task and eye measures. Published normal values for the protocol used in our studies do not exist. Although the subject matter expert (PAW) identified some Normal participants exhibited abnormalities in eye tracking results, none were excluded from the comparisons because all had been carefully screened to be free of mTBI or other potentially confounding neurologic conditions. Differences between the mTBI and Normal groups remained despite this increase in variability. Our study shows

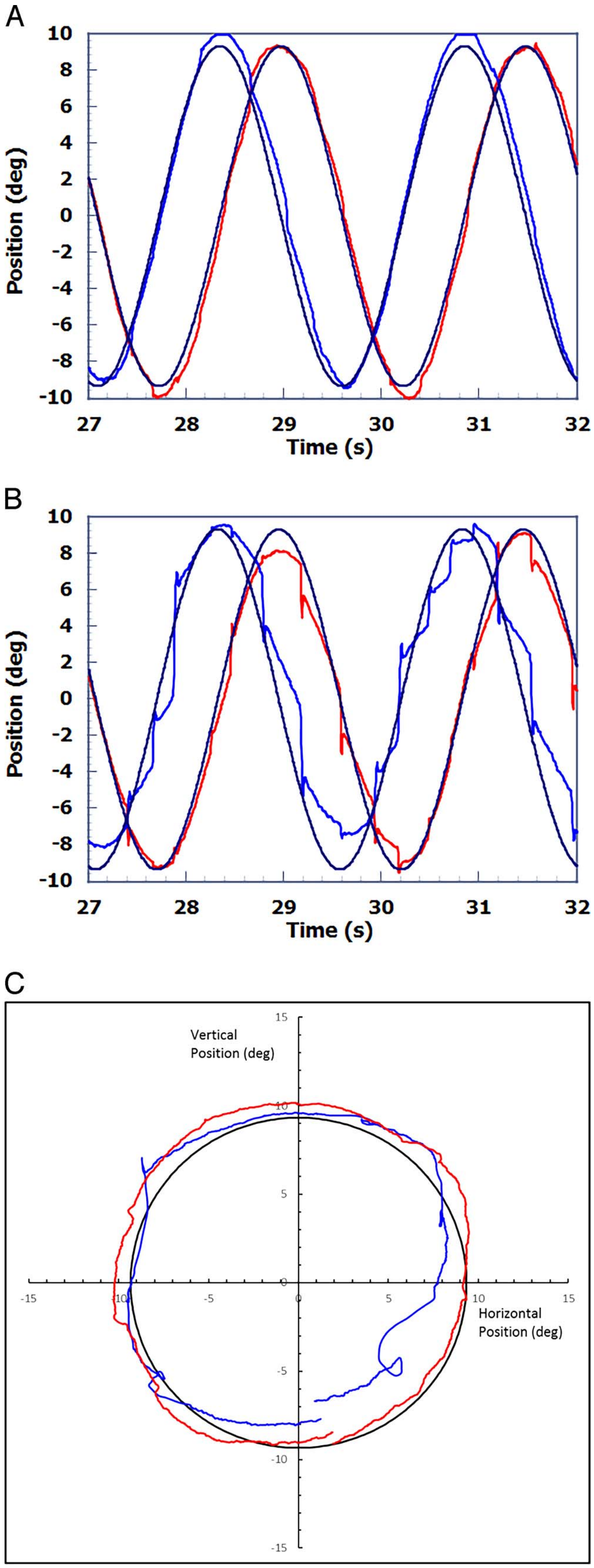

Figure 1. Illustration of comparative performance of a BIMA and Normal participant on the circular task. (**A**) Circular task–Normal participant (N2311): horizontal component (*red*) and vertical component (*blue*). (**B**) Circular task–BIMA participant (B0041): horizontal component (*red*), vertical component (*blue*). *Individuals with mTBI produced larger amplitude saccadic corrections and shorter durations of smooth pursuit. (**C**) Combined polar plot of same data during circular tracking for Normal control (*red*) and mTBI participant (*blue*).

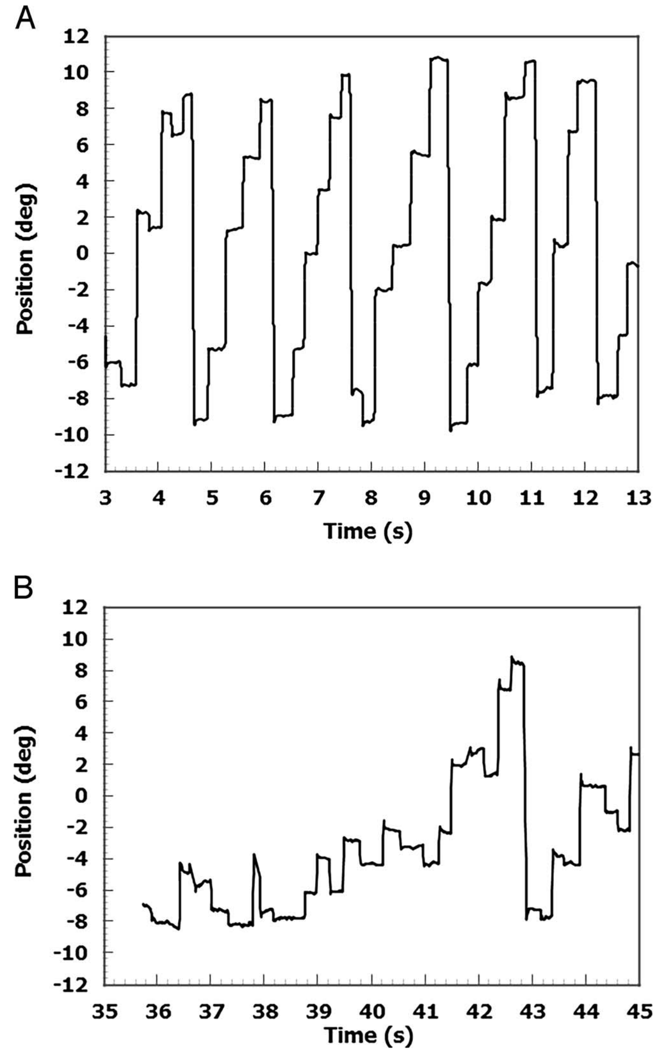

Figure 2. Illustration of comparative performance of a BIMA and Normal participant on the reading task. (**A**) Reading task–Normal participant (N1011). (**B**) Reading task–BIMA participant (B0401). *Compared with Normal participants, BIMA participants read fewer lines per unit time, produced more regressions and more total number of fixations, and had smaller amplitude forward saccades. As shown here, the same duration of time is presented (10 seconds) and the Normal participant reads about six lines, whereas the BIMA participant completes just over one line of text.

that most statistical significance among the eye measures occurred during circular tracking, followed by reading, horizontal and vertical step, and horizontal ramp tracking.

For the circular task, the oculomotor system must generate simultaneous equal amplitude sine and cosine neural signals that drive the extraocular muscle pairs of the eye. To further demonstrate the complexity of the response, both the horizontal and vertical neural signals to the eye muscles must vary sinusoidally during pursuit. In addition, corrective saccades must be programmed for both the horizontal and vertical position of the eyes. For the horizontal and vertical ramp tasks, the smooth pursuit system is also involved;

however, the response is only one-dimensional. In both cases, positional errors were likely to be reduced by corrective saccades. The significantly lower intersaccadic interval velocity seen in the horizontal ramp task is consistent with a lower gain in tracking. The significantly different performance of BIMA participants compared with Normal participants suggests vulnerability or sensitivity of the smooth pursuit system to mTBI compared with the areas of the brain thought to be involved with the saccadic system, which include the supplementary efferent field, frontal eye field, posterior parietal complex, dorsolateral pontine nucleus, medial superior temporal, medial temporal, dorsomedial pornine nucleus, nucleus reticularis tegmenti pontis, and paraflocculus.[6,24] The finding of no difference between BIMA and Normal participants of the main sequence profiles is consistent with the finding of others.[25]

The ability to effectively read requires an intact oculomotor control system, as well as preserved cognitive resources. Reading appeared to be a sensitive indicator in our population of mTBI participants, resulting in reduced saccadic amplitudes, more fixations per line, increased numbers of regressions per line, and fewer lines read. The saccadic amplitudes when reading were significantly less, meaning that fewer character spaces were being processed per fixation. Compensating for the reduced saccadic amplitudes requires a concomitant increase in the number of saccades and fixations needed to read a line of text, likely resulting in slower overall reading speed. BIMA participants also showed an increased number of regressions per line compared to Normal participants. The reduced saccadic amplitudes and increases in the number of fixations and regressions per line may also be related to oculomotor effects as well as cognitive and memory related issues. These results are consistent with Ciuffreda et al.,[23] who showed slower reading times, increased regressions, and smaller amplitude saccades on average in TBI patients.

Previous studies have examined eye movement responses after an mTBI and these studies, with smaller sample sizes than the BIMA and Normal studies, reported lower target prediction[26] and decreases in performance on smooth pursuit tasks (Jacobs and Skelly. *IOVS* 2013;54:ARVO E-Abstract 1921). The latter report included only 11 controls and 11 mTBI participants, and the differences were not statistically significant. Cifu et al.[15] reported mTBI participants tracked stepwise moving targets less accurately than normal controls. Measures thought to be comparable between the EyeLink 1000 and the EyeLink II include number of fixations and saccades, smooth pursuit durations, average saccadic amplitudes, measures of fixation stability, and pursuit velocities. Measures that cannot accurately be compared between studies due to occasional transitory postsaccadic oscillation include saccadic peak velocity, peak acceleration and deceleration, and saccadic duration.[27]

The results from this study represent the largest sample of well-characterized symptomatic participants following mTBI and normative controls measured on the EyeLink 1000 reported to date. Good separation between the BIMA and Normal groups was observed across several tasks and functional measurements. Our findings support measures of smooth pursuit, horizontal and vertical step, and reading tasks as potential outcome measures in future studies of brain-injured individuals. An analysis of follow-up performance will clarify the within-person variability across time and the potential role of this modality in measuring and tracking abnormalities associated with mTBI over time and provide information about whether there is potential for the measures to be responsive to therapy.

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