Fixation Stability as a Biomarker for Differentiating Mild Traumatic Brain Injury from Age Matched Controls in Pediatrics

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Traumatic brain injury (TBI) is an increasingly significant health concern worldwide, compounded by the difficultly in detection and diagnosis. Fortunately, a growing body of research has identified oculomotor behavior, specifically saccades and smooth pursuit eye movements as a promising endophenotype for its reflection of the abnormalities of neurocircuitry. However, there is one variable in particular - fixation stability – that may also help further indicate the presence of TBI. To date, limited research exists using fixation stability to indicate the presence of a mild TBI (mTBI), especially in the pediatric population. The present study examined data from 91 individuals clinically diagnosed with mTBI and a further 140 age and gender matched controls. They all completed the RightEye fixation stability test using a remote eye tracker. Results were analyzed using one-way univariate ANOVAs, ROC analysis and stepwise logistic regression. The results indicated that fixation stability is detrimentally impacted by mTBI in pediatric patients, and the oculomotor test can be used to differentiate between those with and without an mTBI.

Introduction

Traumatic Brain Injuries (TBIs) are a public health concern with around 1.7 million people diagnosed with one every year[1]. Ninety percent of those are classified as mild[2,3]. Oculomotor research contributes to the growing understanding of TBI by providing insight into neural functioning for clinicians and scientists[4]. Oculomotor behavior is a promising neuropsychological endophenotype, as it reflects the abnormalities of complex neurocircuitry[4]. Specifically, oculomotor impairments can be mapped to the location of neural dysfunction and offer objective examination of neurological health[5]. Oculomotor behavior is commonly broken down into the following eye movement categories: smooth pursuits, saccades, and fixations[6]. Smooth pursuits occur when the eyes track a moving stimulus to stabilize the image on the fovea, a site of high visual acuity[7,8,9]. Saccades are rapid movements of the fovea between fixation points[10]. Finally, fixations keep the eye position in a relatively still state to hold the image of a stationary target on the fovea[11].

Depending on the type of eye movement, different brain regions become activated[12]. For example, fixations involve specific cerebral and brainstem structures[11]. These cerebral structures include the Parietal Eye Field (PEF), the Supplementary Eye Field (SEF), middle temporal and medial superior temporal areas, and the dorsolateral prefrontal cortex[12]. Additionally, the Frontal Eye Field (FEF) neurons fire at the beginning of and during fixations[13]. The brainstem also impacts fixations and includes the substantia nigra pars reticulata of the basal ganglia and the rostral pole of the Superior Colliculus (SC)[10]. Examining the neurocircuitry regulating oculomotor behavior is valuable to understanding both normal functioning and the pathophysiology of diseases and injuries, including concussion[16,17].

Currently, the severity of a TBI is categorized as mild, moderate, or severe, depending on a patient's Glasgow Coma Score (GCS)[1]. The GCS evaluates a patient's level of consciousness using a scale that rates a patient's best motor response, best verbal response, and eye opening ability[14]. Mild

TBI (mTBI) is the most common form of TBI and includes brain injuries from blows to the head or body that induce neurological symptoms[1,18]. The GCS is one of the most widely used clinical classification for head injury[19], however it is a poor discriminator in mild cases[20] and is less useful in pediatric measures[21]. Current tests for TBI include a physical exam with symptom reports, neurological testing such as the Standardized Assessment of Concussion or Defense Automated Neurobehavioral Assessment (DANA), and vestibular assessments such as the Balance Error Scoring System (BESS). A sensorimotor examination is also part of a standard clinical assessment for concussion and may include the King-Devick Test (KDT) which evaluates saccades or the Vestibular/Ocular Motor Screening (VOMS) which provides a more complete assessment of eye movements to help clinicians evaluate vestibular and ocular abnormalities after TBI[22]. The VOMS tests saccades, smooth pursuits, fixations, convergence, and the vestibular-ocular reflex[18]. Although it can distinguish TBI athletes from healthy controls, the VOMS relies on subjective reports of symptoms that may introduce error from recall bias and underreporting[23]. Also, the VOMS cannot detect specificity beyond gross eye movement observation by the clinician[23]. It is therefore important to implement more objective and specific methods to assist in diagnostic decision making.

Eye-tracking technology quickly delivers precise, objective eye movement recordings by surveying the eye several times per second[5,16,17]., Examining damaged circuits from TBI with oculomotor assessments produces quantifiable data to complement existing TBI screening methods[24,25]. Visual fixations require less complicated neural coordination than other eye movements and eye tracking may become a simple, reliable tool for studying oculomotor deficits from TBI[14]. Furthermore, loss of fixation is seen as a significant problem for people with TBI. According to the research undertaken by Lemke and colleagues[26], loss of fixation was found in 29% of baseline testing for veterans with TBI from combat blast exposure. A loss of fixation has significant lifestyle implications such as falling, and impaired coordination[13]. Lemke and colleagues'[26] baseline testing is further

validated via clinical observation. A lack of fixation stability was observed by Arbour and colleagues[14] when studying TBI patients in the Intensive Care Unit (ICU). Nurses assessed visual fixation by observing a patient's ability to maintain mutual gaze. Patients unable to fixate within 24 hours of ICU admission performed poorer on attention tasks and had more volume loss in the SEF and midbrain compared to patients able to fixate. In another study, using a patient questionnaire, Brahm and colleagues[27] studied military outpatients and identified fixation instability in patients with blast-related TBI. Patients in these studies were all adults with moderate to severe TBI. To date however, most research examining oculomotor behavior in people with TBI has focused on saccades and smooth pursuit eye movements[28]. In the most recent meta-analysis by Mani et al[28], whose purpose it was to conduct a review of literature from papers that objectively measured the effect that TBI has on oculomotor behavior, saccades and smooth pursuit eye movements were the only eye movements evaluated, likely due to the lack of research in fixations.

In clinical examination and clinical studies using questionnaires fixation stability is a standard part of the oculomotor exam[29]. The gap between clinical practice and research reveals the need for examination of fixation stability in a quantifiable manner to determine if this construct helps further differentiate TBI patients, especially mTBI which are the most difficult to diagnose, from those with no history of TBI and pediatrics. This study was conducted to add another element, specifically fixations, to the already important analysis of oculomotor behavior for examining mTBI. Introducing novel discriminatory measures relative to fixation assessments, provides a less complicated measure of performance and thus represents a reliable and simple scheme of detection and analysis of oculomotor deficits associated with brain injury. Metrics for quantifying fixations include measurements of Bivariate Contour Ellipse Area (BCEA), Convergence Point, Depth, Disassociated Phoria, and Targeting Displacement[30]. Due to the elliptical nature of fixation points, x and y coordinates are used to find an ellipse that fits the central set of x and y data points for left right and both eyes[31].

Microsaccades and drifts of the human eye cause corrections of the eye back to a central point. These slight eye movements form an area of dispersion in the shape of an ellipse that is measured by the BCEA[32,33]. A larger BCEA indicates a less stable fixation. Impaired fixation stability may indicate dysfunction in brainstem lesions affecting the Nucleus Prepositus Hypoglossi-Medial Vestibular Nucleus Region (NPH-MVN) which is essential for neural integration and vestibular imbalance[34,35].

Convergence point is the average distance between the "point of convergence of eyes" from the stimuli location on z-axis in a 3D plane. This can be eso (converging before the stimuli) or exo (converging after stimuli). Depth is the ability to see in three dimensions and arises from binocular depth cues such as stereopsis, where differences between the images from both eyes are combined in the cerebral cortex to produce one 3D representation[36]. Depth refers to the difference between the point of convergence and the screen. The ideal result is zero. A negative number shows a point of convergence behind the screen. A positive number shows a point of convergence in front of the screen. Close to zero is best. Disassociated Phoria is the deviation of the line of sight inward (eso +) or outward (exo -). Ideal is no deviation (ortho) and a result of zero. Close to zero is best. Targeting Displacement denotes the displacement between target (FS stimuli) and the mean of gaze points corresponding to that stimuli, on X and Y-axis.

Limited research exists using these fixation metrics to examine TBI in pediatrics, specifically mTBI patients compared to people with no history of TBI using eye tracking technology. DiCesare and colleagues[37] used eye tracking to analyze fixations based on gaze spread. Results showed that TBI patients exhibited greater fixation errors between saccades[37]. In another eye tracking study conducted by Cifu et al., (2015)[29] all fixation data between saccades showed no differences between TBI and no-TBI patients. To date no studies have used eye tracking with stimuli that does not move, therefore isolating fixations in a central point of gaze rather than trying to capture them between saccadic behavior.

The purpose of this study is to add another element, specifically fixations, to the already important analysis of oculomotor behavior for examining mTBI. This study will use a stationary target therefore isolating fixations, while tracking the eyes to accurately and quantitatively determine if fixation stability can differentiate mTBI from persons with no history of TBI.

Methods

Participants

Two-hundred and thirty-one pediatric participants were analyzed. One hundred and sixteen were clinically diagnosed as having a mTBI by a clinician within two days of the assessment. Twenty-five of these participants were excluded (see procedure) leaving ninety-one total participants with mTBI. One-hundred and forty were age- and gender-matched controls. Participants were between the ages of 6-18 years (M = 14.20, SD = 2.78); 165 were males (71.4%), 66 were females (28.6%). Of the 231 participants, 68.8% were White, 3.0% were Hispanic, .4% were Asian, 7.4% were Black, and 20.4% opted not to report ethnicity. The groups were matched by age (See Table 1).

Table 1: Demographic data by Age and Gender

Group (n)	Mean Age (±SD)	Females	Males
No-mTBI (140)	13.31 (2.48)	39	101
mTBI (91)	12.13 (2.97)	27	64

n = Number; SD = Standard Deviation

Clinical Diagnosis of mTBI for Pediatric Patients: All participants had been clinically assessed by Board Certified Neurologists with at least 5 years' experience in diagnosing TBI. Clinical diagnosis of mTBI was based on the American Congress of Rehabilitation Medicine (ACRM) definition[38]. All participants were additionally examined using the GCS and scored between 13-15 on the scale. Although the GCS is widely used it is not necessarily the best measure of pediatric mTBI[21]. Furthermore, clinicians do not usually use imagining for pediatric mTBI cases[39]. Therefore, the Graded

Symptoms Checklist (GSC) in the Standardized Assessment of Concussion (SAC)[40] was also used as a secondary clinical tool for measurement of mTBI as recommended by the Journal of the American Medical Association Pediatrics clinical guidelines[39,41]. Using results from Grubenhoff, Kirkwood, Gao, Deakyne and Wathen (2010)[19] and the American Academy of Neurology (AAN)[42] concussion grading scale, pediatric patients (6-18 years of age) were evaluated as having mTBI if their GCS score was between 7.7 to 19.3. According to Grubenhoff et al., (2010)[19] this yielded a 95% confidence interval for case-patients with an AAN grade 1 TBI (7.7-10.7) or grade 2 TBI (11.5-19.3). Therefore, participants in the mTBI group in this study scored between 13-15 on the GCS *and* 7.7-19.3 on the GCS.

Apparatus

Stimuli were presented using the RightEye tests on a Tobii I15 vision 15" monitor fitted with a Tobii 90Hz remote eye tracker and a Logitech (model Y-R0017) wireless keyboard and mouse. The participants were seated in a stationary (nonwheeled) chair that could not be adjusted in height. They sat in front of a desk in a quiet, private room. Participants' heads were unconstrained. The accuracy of the Tobii eye tracker was 0.4◦ within the desired headbox of 32 cm × 21 cm at 56 cm from the screen. For standardization of testing, participants were asked to sit in front of the eye tracking system at an exact measured distance of 56 cm (ideal positioning within the headbox range of the eye tracker).

Oculomotor Task

The RightEye Fixation Stability oculomotor test included viewing six targets, presented one at a time, for 7 seconds each, with a break of three seconds between targets. Before each target was presented, identical verbal instructions were given to every participant: "Move your eyes to the center of the target. Keep your eyes as still as possible, until the target disappears." The tester then asked, "Are you looking at the center of the target?" Once the participant confirmed with a verbal "Yes" the tester pressed the spacebar and the 7-second time began.

The same order of targets were used for each participant and used in past fixation stability research from Bellmann and colleagues (2004) [33]: Target 1 was a 1° cross, T2 was a 1° filled circle, T3 was a small 4-point diamond (3° point separation) using dimensions as in the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA), T4 was a large 4-point diamond (7° point separation) using dimensions as in the Humphrey Field Analyzer, T5 was large-crossover whole-image diagonal with open 1° center, T6 was a 1° letter x (Figure 1). The following metrics were used to examine fixations; Bivariate Contour Ellipse Area (BCEA), Convergence Point, Depth, Disassociated Phoria, and Targeting Displacement (See Table 2 for further information).

Table 2

Fixation Metrics

Fixation Metrics	**Definition**
Bivariate Contour Ellipse Area (BCEA)	Microsaccades and drifts of the human eye cause corrections of the eye back to a central point. These slight eye movements form an area of dispersion in the shape of an ellipse that is measured by the BCEA.
Convergence Point	The average distance between the "point of convergence of eyes" from the stimuli location on z-axis in a 3D plane.
Depth	The ability to see in three dimensions.
Disassociated Phoria	The deviation of the line of sight inward (eso +) or outward (exo -).
Targeting Displacement	The displacement between target (FS stimuli) and the mean of gaze points corresponding to that stimuli, on X and Y-axis.

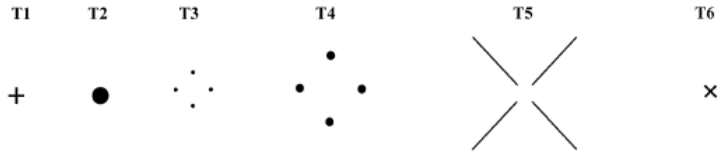

Figure 1. Targets used for Fixation Stability testing. Adapted from Bellmann et al., 2004[43].

Procedure

Participants were recruited through RightEye clinical providers. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocols were approved by the Institutional Review Board of East Carolina University. The nature of the study was explained to the participants and all participants provided written consent to participate. Participants were excluded from the study if they had more than one single discrete episode of mTBI (n = 21). Following informed consent, participants were asked to complete a prescreening questionnaire and an acuity vision screening where they were required to identify four shapes at 4 mm in diameter. If any of the prescreening questions were answered positively and any of the vision screening shapes were not correctly identified, then the participant was excluded from the study (n = 3). Additionally participants were excluded from the study if they reported any of the following conditions, which may have prevented successful test calibration during the prescreening process: this included vision-related issues such as extreme tropias, phorias, static visual acuity of >20/400, nystagmus, cataracts or eyelash impediments or if they had consumed drugs or alcohol within 24 hours of testing (n = 1)[43-47]. Participants were also excluded if they were unable to pass a nine-point calibration sequence. As a result of the pre-screening the total participants excluded from the study was 25.

Qualified participants who successfully passed the nine-point calibration sequence completed the eye tracking tests. The calibration sequence required participants to fixate one at a time on nine points displayed on the screen. The participants had to successfully fixate on at least eight out of nine points on the screen to pass the calibration sequence. Written instructions on screen and animations were provided before each test to demonstrate appropriate behavior required in each of the tests.

Data Analysis

The differences in the groups (Control vs mTBI) were analyzed on clinically verified data using JMP PRO 14.0 (SAS Institute; Cary, NC). The comparison was evaluated using one-way univariate ANOVAs on the fixation stability measures including: Bivariate Contour Ellipse Area (BCEA), Convergence Point (+/- mm), Depth (+/- mm), Disassociated Phoria, and Targeting Displacement. The alpha level was set at $p < 0.05$ and partial eta-squared (η_p^2) was used to determine effect size. In addition, a series of ROC analysis were plotted for the fixation stability variables. Significant area under the curve (AUC) with 95% confidence intervals ($p < 0.05$) was used to indicate the ability of each variable to differentiate concussed participants from non-concussed. A stepwise multivariable logistic regression models were used to assess the relationship between Control and mTBI groups and fixation stability variables: BCEA, Convergence Point (+/- mm), Depth (+/- mm), Disassociated Phoria, and Targeting Displacement scores. Global effect tests were used to determine if a predictor was significant at $\alpha = .05$

Results

The ANOVA results for BCEA demonstrated a significant main effect for Group [$F(1, 229) = 13.453$; $p < .0001$, $\eta_p^2 = 0.236$]. The data revealed a significant difference between mTBI group (M = 6.1648, SD = 1.060) and the Control group ($M = 5.64$, $SD = 1.062$). The ANOVA results for Convergence Point demonstrated a significant main effect [$F(1, 229) = 21.094$; $p < .0001$, $\eta_p^2 = 0.29$] and Depth [$F(1, 226) = 5.785$; $p < .001$, $\eta_p^2 = 0.153$]. Further, the data demonstrated a significant effect for Disassociated Phoria [$F(1, 226) = 5.48$; $p = .017$, $\eta_p^2 = 0.26$]; however, Targeting Displacement [$F(1, 224) = 3.381$ $p = .067$, $\eta_p^2 = 0.293$] demonstrated a non-significant difference between Control and mTBI groups (See Table 3).

Table 3: Mean and Standard Deviation for Fixation Stability Variables.

Group (n)	BCEA	Convergence Point	Depth	Disassociated Phoria	Targeting Displacement
mTBI	6.16 (1.06)	621.04 (89.96)	-23.62 (76.11)	-0.621 (2.407)	-0.373 (2.180)
Control	5.64 (1.06)	574.07 (79.19)	-2.46 (57.31)	-0.0571 (1.232)	-0.008 (0.704)

Multivariable Logistic Regression

A stepwise multiple logistic regression analysis was conducted to evaluate how well the criterion variable TBI status predicted fixation stability. The predictors were the five fixation stability indices BCEA, Convergence Point, Depth, Disassociated Phoria, and Targeting Displacement scores, while the criterion variable was TBI status. The linear combination of BCEA, Convergence Point, and Depth was significantly related to the TBI status, $\chi^2 = 34.77$; $p < 0.0001$, Nagelkerke $R^2 = .189$. The other two predictors, Disassociated Phoria, and Targeting Displacement scores, did not significantly contribute to the model and were removed (See Table 4). The final model accurately predicted 68.4% of TBI status, with sensitivity of 65% and specificity of 70% (See Table 5).

Table 4: Estimated results for model coefficients: B, Exp(B), confidence intervals and levels of significance in the logistic regression models

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1	Convergence Point	-0.008	0.002	17.272	1	0.000	0.992
	Constant	5.333	1.191	20.062	1	0.000	207.026
Step 2	BCEA	-0.416	0.141	8.697	1	0.003	0.660
	Convergence Point	-0.008	0.002	14.414	1	0.000	0.992
	Constant	7.463	1.453	26.372	1	0.000	1741.730
Step 3	BCEA	-0.404	0.141	8.227	1	0.004	0.668
	Convergence Point	-0.015	0.004	14.194	1	0.000	0.986

Depth	-0.010	0.004	4.801	1	0.028	0.990
Constant	11.397	2.408	22.405	1	0.000	89022.838

Table 5: Sensitivity and Specificity statistics of model 3 including BCEA, Convergence Point, Depth as predictors for TBI Status.

Statistic	**Value**	**95% CI**
Sensitivity	65.00%	51.60% to 76.87%
Specificity	70.00%	62.11% to 76.38%
Positive Likelihood Ratio	2.14	1.59 to 2.87
Negative Likelihood Ratio	0.50	0.35 to 0.72
Disease prevalence (*)	25.97%	20.44% to 32.13%
Positive Predictive Value (*)	42.86%	35.88% to 50.13%
Negative Predictive Value (*)	85.00%	79.83% to 89.03%
Accuracy (*)	68.40%	61.98% to 74.34%

Discussion

The purpose of this study is to investigate differences in groups (mTBI versus Control) between the fixation stability test measured by BCEA, Convergence Point, Depth, Disassociated Phoria, and Targeting Displacement scores. BCEA results revealed significant differences between groups with the mTBI group showing a larger gaze spread, indicative of less ability to keep the eyes close to the target without deviating. A larger BCEA indicates a less stable fixation. Impaired fixation stability may indicate dysfunction in brainstem lesions affecting the Nucleus Prepositus Hypoglossi-Medial Vestibular

Nucleus Region (NPH-MVN) which is essential for neural integration and vestibular imbalance[34,35]. These results are consistent with research from Arbour and colleagues[14] who studied concussion patients in the ICU and observed an inability to hold a fixation within 24 hours of admission and DiCesare and colleagues[28] and Lemke and colleagues[29]. Results of this study expand this past research which included only moderate and severe TBI. Furthermore, DiCesare and colleagues[37] and Lemke and colleagues[29] examined adults only. Nevertheless, fixation was found to be impeded in these studies where fixation loss was reported in 29% of eyes in initial testing. Further evidence by Brahm and colleagues[27], found patients with mild and severe concussion identified fixation instability as a symptom on average 8 and 10 percent respectively. This study was conducted using adults, nevertheless providing further evidence, consistent with this study, that fixations may be impeded from a TBI. Results from the BCEA analysis were most promising as a differentiating factor between the mTBI and Control groups in pediatric patients.

Results for Convergence Point and Depth and Disassociated Phoria also proved significant. Such eye movements used to converge, coordinate and hold the eyes while maintaining fusion involve complex neurological processes that may be impacted in persons with TBI. These metrics result in problems with binocularity, reading problems, balance, coordination and near-work functions. Vergence has presented as dysfunctional between 24-63.6% of the time in retrospective studies outlined in a review by Thiagarajan, Ciuffreda & Ludlam (2011)[44]. Furthermore, general oculomotor dysfunction was found in anywhere from 40-90% of patients in the same retrospective review. Stereoacuity (a related concept to the depth metric in this study) was found to be statistically significantly poorer in patients with mTBI compared to Controls[44]. In contrast Ciuffreda, Yadav, Ludlam, Peddle, Hulse, Walter, Han (2012)[45], found that patients with mTBI whose symptoms of poor depth perception was not due to binocular vergence or a slightly reduced stereoacuity and speculated that this was a problem reflecting a higher-level cortical perceptual phenomenon related to diffuse brain damage in areas dealing

with visuo-spatial mapping. Contrasts in these results warrant further research specifically in pairing symptoms with sensitive quantifiable measurements such as eye tracking. Furthermore, age should be considered in future research as Ciuffreda, Yadav, Ludlam, Peddle, Hulse, Walter, Han (2012)[45] examined adults only. A small sample size (n=10) may also contribute to inconclusive results. Collectively these five-fixation metrics were found to predict mTBI at 68.4% with 65% and 70% sensitivity and specificity. Although not a highly predictive number by themselves, when combined with other oculomotor behavior such as saccades and pursuits this may prove to further improve the predictive nature of oculomotor behavior as a biomarker for mTBI. Nevertheless, results from this study broadly concur with other research findings suggesting that oculomotor behavior is affected by mTBI. Results of this study are also in agreement with past research where fixations stability as measured by BCEA and vergence (as measured by the Convergence Point) are detrimentally impacted by a mTBI.

This study was the first to examine fixation stability in mTBI pediatric patients. Future research should examine adults, specifically those over 65 who are the second largest group of persons who incur mTBIs and is describe as the "silent epidemic" in older adults. According to Thompson, McCormick & Kagan (2006)[46] "the relative neglect of these variables in neuroscience research may partially explain why predicting outcomes and providing care in the older adult population with TBI remains so problematic." Future research in TBI should consider fixations alongside saccades and pursuits to a) have a more complete assessment of oculomotor behavior and b) to potentially be able to differentiate the brain location associated with such dysfunction[47].

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