

Vertical Smooth Pursuit as a Diagnostic Marker of Traumatic Brain Injury

Melissa Hunfalvay, Chief Science Officer, RightEye LLC, 7979 Old Georgetown Rd, Suite 801, Bethesda, MD 20814, U.S.A. (301) 979 7970 melissa@righteye.com

Claire-Marie Roberts, Research Fellow, University of the West of England, Coldharbour Lane, Bristol, BS16 1QY claire-marie.roberts@uwe.ac.uk

Nicholas P. Murray, Professor, East Carolina University, Department of Kinesiology, Minges Coliseum 166, Greenville, NC 27858, U.S.A. (252) 737 2977 murrayni@ecu.edu

Ankur Tyagi, Data Scientist, RightEye LLC, 7979 Old Georgetown Rd, Suite 801, Bethesda, MD 20814, U.S.A. (301) 979 7970 ankur@righteye.com

Kyle William Barclay, Student, Case Western Reserve University, 10501 Streamview Court, Potomac, MD 20854, (240) 743 9715, kwb37@case.edu

Takumi Bolte, Senior Computer Scientist, RightEye LLC, 7979 Old Georgetown Rd, Suite 801, Bethesda, MD 20814, U.S.A. (301) 979 7970 takumi@righteye.com

Hannah Kelly, Emory University, 201 Dowman Dr, Atlanta, GA 30322, U.S.A. (301) 706-0876 hmkelly@emory.edu

Frederick Robert Carrick, Bedfordshire Centre for Mental Health Research in Association with University of Cambridge, Cambridge, United Kingdom; ²Neurology, Carrick Institute, Cape Canaveral, FL, United States; ³Harvard Macy Institute and MGH Institute of Health Professions, Boston, MA, United States. drfrcarrick@post.harvard.edu

*Please direct all correspondence to Dr. Claire-Marie Roberts

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

Abstract

Background: Eye tracking tests to measure vertical smooth pursuit as a proxy for neural deficits associated with traumatic brain injury (TBI) were evaluated in the present study.

Methodology: 92 participants reporting either no TBI, mild, moderate or severe TBI participated in an automated test of vertical smooth pursuit performance using a remote eye tracker.

Results: The vertical smooth pursuit eye tracking test was able to distinguish between severe and moderate levels of TBI but was unable to detect differences in the performance of participants with mild TBI (mTBI) and healthy controls.

Conclusions: The results indicated that using eye-tracking technology to measure vertical smooth pursuit metrics offers a swift, objective, reliable and quantifiable way of differentiating between individuals with severe and moderate levels of TBI.

Key words: *eye tracking, vertical smooth pursuit, TBI, concussion*

Introduction

The rising incidence of traumatic brain injury (TBI) is a public health concern and a significant cause of morbidity and mortality. In the United States alone, about 1.7 million people suffer from a TBI every year, and 52,000 of these cases result in death.¹ Oculomotor research contributes to the growing understanding of TBI by providing insight into neural functioning for clinicians and neuroscientists.² Oculomotor behavior is a promising neuropsychological endophenotype, as it reflects abnormalities of complex neurocircuitry.² Specifically, oculomotor impairments can be mapped to the location of neural dysfunction and offer objective examination of neurological health.³

Oculomotor behavior encompasses the following eye movement categories: fixations, saccades, and smooth pursuits.⁴ Fixations hold the eye relatively still to keep the image of a stationary target on the fovea, a site of high visual acuity.⁵ Saccades quickly move the fovea between fixation points,⁶ and smooth pursuits track a moving stimulus to stabilize the image on the fovea.^{7,8,9} Depending on the type of eye movement, different brain regions become activated.¹⁰ For example, the smooth pursuit pathway in primates begins with M retinal ganglion cells, neurons that process motion information and transmit signals from the lateral geniculate nucleus to V1/striate cortex.¹⁰ Visual information then flows from striate to extrastriate areas that project to the brainstem and other cortical and subcortical areas, including the Frontal Eye Field (FEF) and Supplementary Eye Field (SEF) in the frontal lobe, Middle Temporal (MT) and Medial Superior Temporal (MST) areas, the intraparietal and posterior parietal cortices, and parts of the cerebellum.¹⁰ Furthermore, smooth pursuit eye movements activate certain brain regions based on the direction of visual stimuli. For horizontal stimuli, areas MT and MST and the FEF project to the Dorsolateral Pontine Nuclei (DLPN), which sends projections to the cerebellum.¹⁰ Cerebellar structures then project to the Medial Vestibular Nucleus (MVN) in the brainstem.¹⁰ The pathway for vertical pursuits resembles that for horizontal, except it includes the rostral nucleus reticularis tegmenti pontis instead of the DLPN.¹⁰ Also, instead of the MVN, the vertical circuitry

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

involves the y-group nucleus and its projections.¹⁰ In tests of circular smooth pursuits while subjects track a moving target on a curved path, fMRI studies have shown bilateral activation of the visual cortex, areas of the parietal cortex, area MT, and some activation in the FEF.¹¹ Examining the neurocircuitry regulating oculomotor behavior is valuable to understanding both normal functioning and pathophysiology, since various injuries and neurological diseases can impair smooth pursuit performance, including TBI.¹²

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 3-15 point scale that rates a patient's best motor response (6 points), best verbal response (5 points), and eye opening ability (4 points).¹³ Mild TBI (mTBI) is defined by a GCS between 13 and 15, moderate between 9 and 12, and severe between 3 and 8.¹ MTBI is the most common form of TBI and includes concussions, or brain injuries from blows to the head or body that induce neurological symptoms.^{1,14} Common concussion tests include symptom evaluations and neuropsychological testing used for injury management.¹⁵ While quick and convenient, symptom reports are subjective, vulnerable to underreporting, and may have limited long-term value, since cognitive and visual deficits can endure after symptoms diminish.¹⁵ The standard test for concussion is the Sport Concussion Assessment Tool (SCAT-3), which involves a physical exam, the GCS, and cognitive and sensorimotor evaluations.¹⁶ This testing battery includes other tests, such as the Standardized Assessment of Concussion (SAC) and the Balance Error Scoring System (BESS); however, none of these specifically test vision.¹⁷ The Defense Automated Neurobehavioral Assessment (DANA) is a new mobile phone application that consists of cognitive and psychological tests to rapidly and reliably identify cases of TBI.¹⁸ Yet, neuropsychological tests, such as DANA, have the potential for patient motivation to affect results.^{19,20} Finally, the King-Devick Test (KDT) includes an evaluation of saccades but does not examine other eye movements often impaired after TBI.^{16,17} The Vestibular/Ocular Motor Screening (VOMS) provides a

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

more complete assessment of eye movements to help clinicians evaluate vestibular and ocular abnormalities after concussion.²¹ The VOMS tests saccades, smooth pursuits, fixations, convergence, and the vestibular-ocular reflex.¹⁵ Although it can distinguish concussed athletes from healthy controls, the VOMS relies on subjective reports of symptoms that may introduce error from recall bias and underreporting.¹⁷ Additionally, the VOMS cannot detect specificity beyond gross eye movement observation by the clinician.¹⁷ One notable exception to the slew of tests that fail to consider eye movements is OVRT or Oculomotor Vestibular Reaction Time test battery. Though OVRT contains an impressive array of diagnostic tools, it does not consider vertical smooth pursuits.²⁷ While it does consider horizontal smooth pursuits, they do not activate the same brain regions as vertical smooth pursuit, and thus information about a particular brain region is not considered.^{10,11}

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.⁷ Examining damaged circuits from TBI with oculomotor assessments produces quantifiable data to complement existing TBI screening methods.^{22,23} Because the widespread cortico-cerebellar circuits involved in smooth pursuits are easily compromised after TBI, smooth pursuit deficits are important to examine with eye-tracking metrics.²³ Two metrics for smooth pursuits include variance and smooth pursuit percentage (SP%). Variance measures the deviance of a gaze path from the ideal path of a stimulus.²² A smaller spread of gaze positions around the target path indicates better accuracy.²² SP% defines the amount of time spent performing a smooth pursuit with appropriate dispersion and velocity throughout a test. The velocity of the eye should match that of the moving stimulus to minimize position error.¹⁹ Pursuit gain is a common velocity metric that calculates the ratio between eye and target velocity, where a larger gain implies better tracking ability.²⁴

Several studies have revealed deficits in the smooth pursuits of patients with concussion or Post-Concussion Syndrome (PCS).^{25,26,27} These include greater lag during smooth pursuit tracking and lower

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

gain of pursuit velocity in subjects with mTBI and PCS symptoms.^{19,28} To investigate smooth pursuits, researchers often utilize circular tracking tests, a type of predictive visual tracking that necessitates attention and working memory.²² Because such cognitive processes require proper prefrontal cortex functioning and are vulnerable to damage from TBI,²² circular tracking tests can assess deficits in attention following TBI and may enhance the accuracy of traditional TBI screening.^{22,28} Compared to controls, mTBI patients tracking an object in a circular path showed reduced target prediction and increased eye position error and variability.^{29,30} These impairments, moreover, correlated with cognitive deficits.^{29,30} Maruta and colleagues similarly found increased error and variability in gaze position with reduced smooth pursuit velocity in acute mTBI patients on a circular visual-tracking task.²⁴

Although few studies have specifically tested vertical smooth pursuit performance following head trauma, there is evidence of TBI patients displaying impaired vertical pursuits. For example, subjects with symptomatic mTBI demonstrated smaller-amplitude vertical pursuits¹⁹ and reduced vertical smooth pursuit velocity gain.^{19,24} Furthermore, patients with acute PCS symptoms exhibited a more rapid decrease in smooth pursuit velocity gain with increasing stimulus frequency.²⁸ This same patient group also showed reduced vertical gain as compared to horizontal gain for objects moving in a low-frequency range.²⁸ Further studies with larger sample sizes are necessary to increase the reliability and precision of results.^{28,29,30,31} Also, very few studies of oculomotor deficits following TBI have included tests of vertical smooth pursuits, and no studies have concentrated exclusively on pursuits in the vertical direction. Given that different neural circuits control horizontal and vertical smooth pursuits, it is important to thoroughly examine vertical pursuits in TBI patients for a more comprehensive evaluation of the different brain regions implicated in head injury.^{10,12} Thus far, no studies have compared vertical smooth pursuits in healthy subjects to patients with different levels of TBI. The goal of this study, therefore, is to explore differences in vertical smooth pursuits measured by variance and

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

SP% between individuals who have not had a TBI and patients diagnosed with TBI (either mild, moderate, or severe).

Methods

Participants

For the data analysis, 92 participants were considered. Participants were between the ages of 11-79 years ($M = 40.01$, $SD = 16.87$); 49 were males (53.26%), 43 were females (46.74%). Of the 92 participants, 70.65% were White, 7.61% were Hispanic, 5.43% were Asians, 5.43% were Black, and 10.88% opted not to report ethnicity. The groups were matched by age (See Table 1). All participants completed the RightEye Vertical Smooth Pursuit test. There were 23 (25% of total participants in all categories of TBI severity) clinically verified participants in each of the following TBI severity levels: No-TBI, Mild TBI, Moderate TBI, and Severe TBI.

Table 1: Demographic data by Age and Gender

Group (n)	Mean Age (\pm SD)	Females	Males
No-TBI (23)	35.04 (16.84)	5	18
Mild (23)	39.74 (18.54)	12	11
Moderate (23)	42.26 (16.11)	10	13
Severe (23)	43.00 (15.80)	16	7

n = Number; SD = Standard Deviation

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

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

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 $32\text{ cm} \times 21\text{ cm}$ 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

In the Vertical Smooth Pursuit (VSP) test, participants were instructed to track a target stimulus - a white dot 0.2 degrees in diameter at a rate of 25.13 degrees per second, starting from the center of the screen. The dot then moved up and down in a sinusoidal way in the vertical plane in a straight line. For a participant to be considered "on target," they were required to follow the stimuli within an error of 2.4 degrees. A participant could also be ahead or behind a stimulus and can still be labeled as 'following' if they are within an error of 4.8 degrees.

Procedure

Participants were recruited through advertisements placed on the internet, social media, bulletin boards and spread by word of mouth. 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. 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. 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 $>20/400$,

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

nystagmus, cataracts or eyelash impediments or if they had consumed drugs or alcohol within 24 hours of testing.^{32,33,34,35,36} Participants were also excluded if they were unable to pass a nine-point calibration sequence. Less than 1% of the participants fell into these categories.

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 (No-TBI, Mild, Moderate, and Severe TBI) were analyzed on clinically verified data. The comparison was evaluated using one-way univariate ANOVA on the Smooth Pursuit Variance and Smooth Pursuit (%) metrics. As the name suggests, Smooth Pursuit Variance measures the variability in gaze while performing a vertical pursuit task. It is measured as standard deviation (in millimeters) in the average distance of each gaze sample point collected, from its expected ideal position. In other words, it explains the coherence in gaze when engaging in vertical pursuits. Smooth Pursuit (%) is calculated as the participant's eyes follow the target within a velocity range of the target. All such sample points are tallied to get the percentage over total test time. A post-hoc analysis was conducted using Tukey's HSD test, to determine the mean differences and their statistical significance, between each group. The alpha level was set at $p < 0.05$ for all statistical tests. In addition, Receiving Operating Characteristic (ROC), Area Under the Curve, Sensitivity and Specificity were calculated for a logistic regression to predict "No-TBI" Vs "All categories of TBI" (Mild, Moderate and Severe).

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

Results

The ANOVA for smooth pursuit variance metrics revealed significant differences between the groups. Smooth pursuit variance metrics resulted in a significant main effect, $F(3, 88) = 4.52$; $p = 0.005$, $\omega^2 = 0.094$. In addition, the Tukey's HSD test demonstrated significant difference between moderate and severe TBI Groups and the no-TBI group; however, there was no significant difference between mild TBI and the No-TBI Group (See Figure 1).

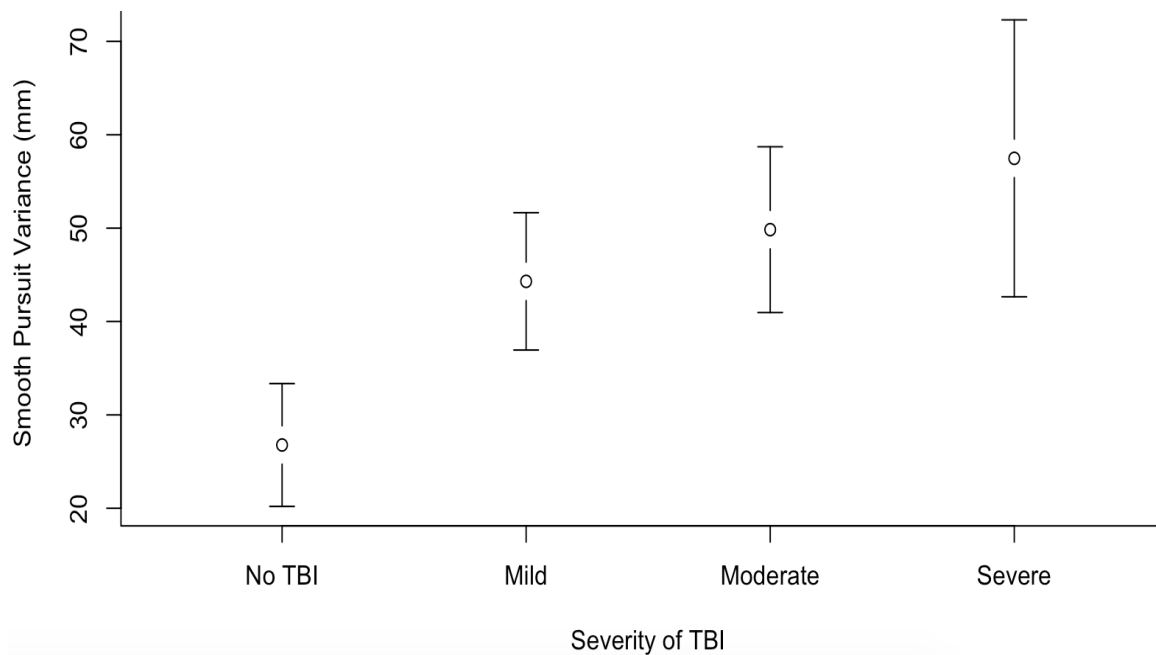


Figure 1: Mean Values of Smooth Pursuit Variance at each level of TBI Severity, with 95% Confidence Interval. For Smooth Pursuit Variance metrics, a lower value is better.

The ANOVA for Smooth Pursuit (%) metrics revealed significant differences between the groups. Smooth Pursuit (%) metrics resulted in main effect, $F(3, 88) = 3.80$; $p = 0.013$, $\omega^2 = 0.094$. In addition, the Tukey's HSD test demonstrated significant difference between moderate and severe TBI Groups and the no-TBI group; however, there was no significant difference between mild TBI and the No-TBI Group (See Figure 2).

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

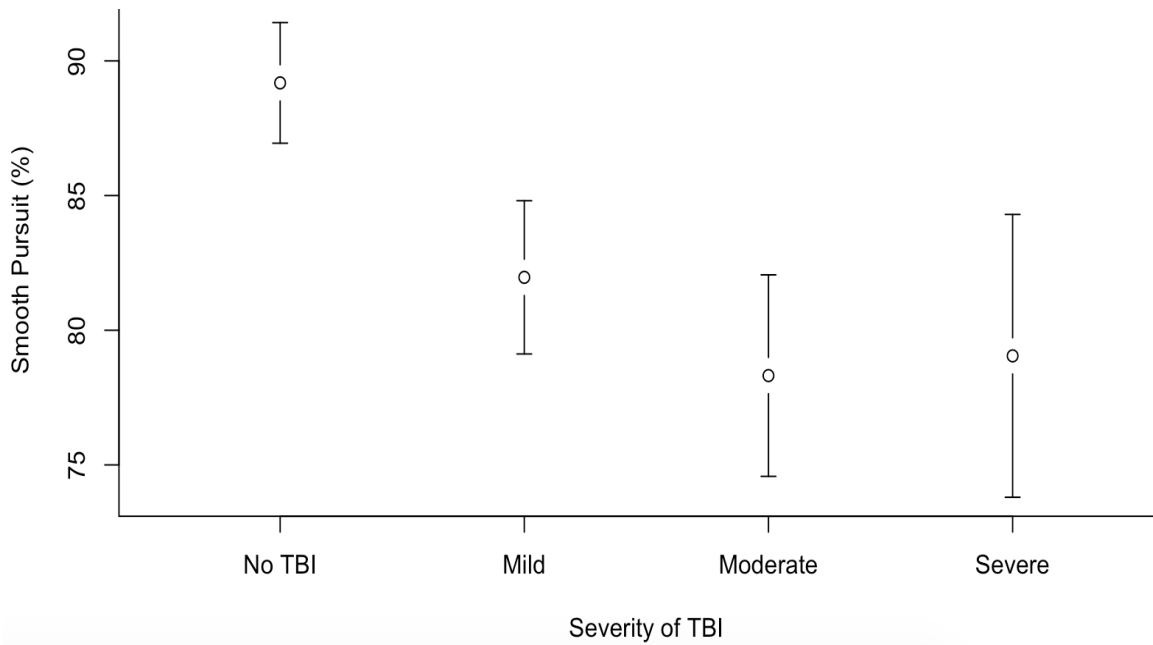


Figure 2: Mean Values of Smooth Pursuit (%) at each level of TBI Severity, with 95% Confidence Interval. For Smooth Pursuit (%) metrics, a higher value is better.

The logistic regression model for smooth pursuit variance and smooth pursuit (%) metrics, revealed differentiated TBI and no-TBI groups. The resulting ROC curve produced an Area Under the Curve (AUC) value of 0.772 with sensitivity = 0.68 and specificity = 0.73 (see Figure 3).

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

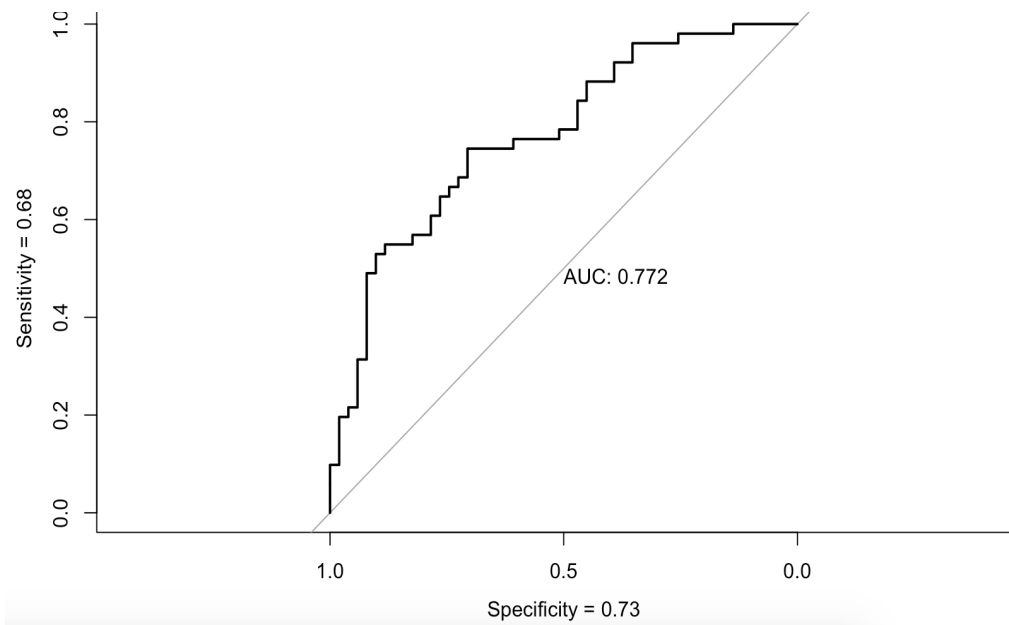


Figure 3: ROC for Vertical Smooth Pursuit (Smooth Pursuit Variance and Smooth Pursuit (%)) – No-TBI Vs TBI

Discussion

This is the first study to use eye-tracking to compare VSPs in healthy subjects to patients with different levels of clinically diagnosed TBI. Compromised smooth pursuits have been linked to TBI in several studies.^{25,26,27} Smooth pursuits are a voluntary behavior and share a neural substrate with attention in the prefrontal cortex.²³ The frontal areas involved in both smooth pursuits and attention are connected to the cerebellum (also involved in smooth pursuits) via a nerve tract that is extremely susceptible to damage from TBI.^{22,23} This relationship explains why many of the symptoms of TBI are associated with functions of the prefrontal cortex.²² Because of this relationship, eye-tracking technology can serve as an indicator of neural dysfunction via eye movements. In this study, variance and smooth pursuit percentage (SP%) were the two metrics used to quantify the eye movements associated with smooth pursuit. Analysis of variance metrics revealed significant differences between TBI groups and control group. Results indicated that eye tracking can be used to distinguish between severe and moderate TBI and control groups, but not mild and control groups. Analysis of SP% metrics

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

also yielded a significant difference between groups along with a main effect. Similar to variance, SP% was able to distinguish severe and moderate groups from control groups but not the mild group. It is interesting that VSPs proved least effective at distinguishing mTBI since the vast majority of literature studies VSPs in mTBI. Other metrics such as horizontal and vertical saccades are able to distinguish even mTBI from control groups, however, these eye movements are controlled by different brain regions.^{10,37} Thus, even though VSPs might not have the highest capacity to differentiate, they are still highly relevant to a holistic model of TBI detection. This is especially true considering variance and SP% were the only two metrics being measured.

The three commonly accepted methods used to diagnose concussion are neurological, vestibular, and oculomotor.¹⁶ Oculomotor can be further divided into types of eye movements including fixations, saccades, and smooth pursuits.⁴ Each of these eye movements depend on different portions of the brain and thus test for different types of brain injury.¹⁰ Even amongst pursuits, vertical and horizontal pursuits differ in their neurological pathways.^{10,11} The eye-tracking diagnostic tool at the center of this study is capable of measuring a number of metrics pertinent to TBI, and has the potential to serve as a very useful adjunct to existing TBI symptoms detection methods. They are a multitude of tests currently used to diagnose concussions, all of which use some combination of the aforementioned diagnostic tools, however most are deficient in at least one of the three categories.¹⁵ For example, the current standard test for concussion in sport is the SCAT-3 which includes a physical exam, GCS and various cognitive and sensory-motor evaluations.¹⁶ Though the SCAT-3 contains a slew of other tests including the Standard Assessment of Concussion (SAC) and Balance Error Scoring System (BESS), it fails wholly to test vision.¹⁷ This inconsistency is not unique to the SCAT-3, the Defense Automated Neurobehavioral Assessment (DANA) is a mobile phone-based assessment uses a cognitive and psychological test to rapidly identify TBI.¹⁸ Unfortunately neurophysiological tests like DANA, and other tests that lack a visual component, create a potential for patient motivation to affect results.^{19,20} Even the King-Devick

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

Test, which measures reading speed, language production, and saccades, fails to consider other eye movements that are often impaired by TBI.^{16,17}

The Vestibular/Orbital Motor Screening (VOMS) is a more holistic method of eye screening for post-concussion abnormalities that tests saccades, smooth pursuit, fixation, convergence, and vestibulo-ocular reflex.¹⁵ Though VOMS can distinguish concussed from non-concussed athletes, it relies on subjective reporting of symptoms that can introduce recall bias and underreporting.¹⁷ In addition, VOMS is somewhat lacking in finesse since it cannot pick up specificity beyond gross eye movements detected by the physician.¹⁷ The Oculomotor Vestibular Reaction Time (OVRT) test battery is a series of tests that has proved very effective at discovering cases of mTBI.^{27, 38} Its wide range of tests considers many of the factors that go into TBI diagnosis. While OVRT does consider smooth pursuit, it only considers horizontal and not VSP.²⁷ Since these eye movements employ different neural pathways, OVRT excludes possibly relevant information by failing to consider VSPs.^{10,11}

Eye-tracking has real potential to fill a void in the world TBI testing. As the only method of objectively and accurately measuring visual behavior, eye-tracking can be used to confirm or deny the presence of TBI's in a unique way. The aforementioned objectivity and accuracy address many of the issues with conventional TBI tests including subjectivity, inaccurate reporting, and issues with patient motivation. Smooth pursuits are just one of the metrics that can be measured using eye-tracking, and even alone they offer great insight into a patient's condition. Though there are many studies looking at differences in smooth pursuit between mTBI and control groups, none compare control groups to three different levels of TBI. This data is just as important as mTBI comparison, and it is important that it is studied. Combined with other metrics, smooth pursuits have real potential to offer a quick and easy to administer TBI detection system. The speed and ease of eye-tracking technology could even prove useful in a sports setting, especially in return to play decisions.

VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

Although eye-tracking represents a great many opportunities, given its infancy as a form of TBI symptom detection, it is recommended that more research be done to amass a broader sample size for comparison purposes. The sample size (n=92) was relatively small, but it was considered adequate for the present studies purposes. Ideally, a more far-reaching study could be done that would encompass a greater geographic area and would include more international diversity with which to compare results.

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VERTICAL SMOOTH PURSUIT AS A MARKER OF TBI

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