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Differential Eye Movements in Mild Traumatic Brain Injury vs. Normal Controls

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Abstract

Objective measures to diagnose and to monitor improvement of symptoms following mild traumatic brain injury (mTBI) are lacking. Computerized eye tracking has been advocated as a rapid, user friendly and field ready technique to meet this need. Eye tracking data collected via a head mounted, video-based binocular eye tracker was used to examine saccades, fixations and smooth pursuit movement in 60 military Service Members with post concussive syndrome (PCS) and 26 asymptomatic control subjects in an effort to determine if eye movement differences could be found and quantified. The diagnosis of mTBI was confirmed by the study physiatrist's history, physical examination, and a review of any medical records. Results demonstrated that subjects with symptomatic mTBI had statistically larger position errors, smaller saccadic amplitudes, smaller predicted peak velocities, smaller peak accelerations, and longer durations. Subjects with symptomatic mTBI were also less likely to follow a target movement (less primary saccades). In general, symptomatic mTBI tracked the stepwise moving targets less accurately, revealing possible brain dysfunction. A reliable, standardized protocol that appears to differentiate mTBI from normals was developed for use in future research. This investigation represents a step toward objective identification of those with PCS. Future studies focused on increasing the specificity of eye movement differences in those with PCS are needed.

Key words: mild traumatic brain injury, post-concussion syndrome, eye tracking, saccades, fixations, smooth pursuit

Introduction

As a result of injuries to both military servicemembers in combat and athletes in contact sports, there has been heightened focus on metrics to diagnose and monitor recovery after mild traumatic brain injury (mTBI) and related sequelae.[1,2] A significant limiting factor in the diagnostic approach to mTBI has been the dependence on self-report of injury and symptoms, resulting in a provisional syndromic-based diagnosis, post-concussion syndrome (PCS). Increasingly there has been recognition that an mTBI is more accurately termed as a "potentially concussive event" (PCE), rather than a syndrome.[3-5] If specific criteria (e.g., alteration or loss of consciousness with associated memory loss/amnesia surrounding the event) are confirmed, then the diagnosis of mTBI may be made. If these criteria are not met, then the PCE cannot be labeled as an mTBI, but may still manifest with symptoms related to secondary physical injury (e.g., neck or skull-based musculature and other soft-tissue) and psychological trauma (e.g., acute stress reaction). It is more proper to apply the "syndrome" label only after the mTBI has been confirmed and has manifest in a symptom complex that has persisted for more than three months after injury.[6] Importantly, even in the case of a confirmed mTBI, the effects of other physical and psychological conditions often contribute to the symptoms and syndrome.[5]

The limitations of the current self-reported, subjective accounting of traumatic events, symptoms, and improvements are manifold. Without objective documentation of the PCE, such as pre-event neuropsychological screening, event videotaping, or data from accelerometers, these potential confounders include: altered or imprecise recall of event duration, severity, and date of occurrence, potentially inaccurate estimation of pre-event functioning, impact of acute stress response, and motivation (positive or negative) to accurately report symptoms. These factors are further influenced by the elapsed time between the event and medical assessment of the subject.

This is important at both the proximal (e.g., secondary factors surrounding the event or trauma that resulted in the PCE, acute recognition of PCE and/or mTBI, acute management of PCE/mTBI) and distal (e.g., increasing inaccuracy of precise recall weeks, months, or even years post-event, subsequent symptoms that arise after PCE, recognition, acknowledgement, and eventual assessment of the PCE/mTBI, ongoing management of the PCE and subsequent symptoms) ends of the encounter with the medical professional.

In addition to the use of self-reported injury events and post-injury symptoms, cognitive screens and more comprehensive neuropsychological testing have predominantly been utilized to diagnose and monitor recovery after mTBI. While this approach is well validated and has proven clinically useful, it also has a number of inherent limitations. Principal criticisms of the testing approach include the subjectivity of self-report, patient fatigue and motivation factors, practice effects, and influence of co-morbid conditions (e.g., pain, anxiety, depression, substance abuse). Additionally, testing batteries often vary in composition based on the practice patterns of individual clinicians, limiting the ability to compare across time and testing centers, with subsequent limitations on meaningful meta-analysis. There is no universally accepted neuropsychological testing battery after PCE.

There is increasing enthusiasm to rely on objective measures to determine the relationship of both a PCE to an mTBI and an mTBI to persistent symptoms. There are few well-designed, large scale studies examining early brain changes following mTBI using diagnostic devices, although many devices and techniques for objectively measuring the brain have been proposed and examined. Some involve measures of brain activity (e.g., electroencephalography [EEG], evoked responses)[7-9], structure (diffusion tensor imaging [DTI], high density fiber tracking [HDFT])[10-12], hemodynamics (e.g., near-infrared spectroscopy [NIRS], transcranial

Doppler ultrasound [TCD])[13-15], and functional testing (e.g., computerized posturography, computerized tests of cognition and executive function)[16-18]. Other efforts have focused on devices that attempt to measure intracranial pathology, such as intracranial hypertension via observation of extracranial phenomena (e.g., optic nerve sheath diameter [ONSD] or otoacoustic emissions).[19] Despite the vigor of studying the utility and validity of these diagnostic approaches, none have achieved a level of efficacy to be considered as the "gold standard," and multidimensional approaches using diagnostic algorithms have not been developed.

One method for the objective assessment of the brain after PCE and mTBI that has shown promise as a user friendly, low cost, non-invasive, definitive approach is eye tracking. Eye tracking has been advocated as a rapid, convenient, and portable (i.e., field ready) method of evaluation However, specific research on its specificity and sensitivity is sparse in this population. Although specific values are not universally presented,[20] one study suggested that the sensitivity and specificity of eye tracking paradigms reaches 100% when differentiating controls from mTBI, or even differentiating PCS from non-PCS in a suspected mTBI population.[21] These results have not been replicated. Previous reports have shown the primary oculomotor deficits in mTBI to be difficulty reading (oculomotor specific), vergence, accommodation, and saccadic gain abnormalities.[22] Eye tracking assessment typically involves the examination of saccades, fixation, and smooth pursuit eye movements (SPEM). Saccades (rapid, accurate, ballistic shifting of gaze to a new area of interest) are studied because they require the complex coordination and timing of neural circuitry in numerous different brain areas, including primarily the frontal lobe, basal ganglia, superior colliculus, and the cerebellum; and would therefore be likely to be sensitive indicators of injury to one of these areas.[23] Further, the various parameters (e.g. direction, gain, velocity, trajectory, etc.) of saccades are "programmed" independent of each

other, generally free of cognitive influence, and can be studied both separately and in combination.[23] Up to the present, fixation (maintaining an image of interest on the fovea) data have not been well studied in TBI patients, largely due to the technical challenges in measuring fixations, and the prevailing belief that the fixations themselves are "silent," offering no meaningful data. Fortunately, the technological limitations have been largely overcome with the latest generation of measurement tools and applied analyses. The "silent" nature of fixation deficits seems likely more an under appreciation of the linkage between subtle (often difficult to measure) visual processing deficits and a range of functional tasks (e.g., reading, driving) or somatic complaints (e.g., headache, dizziness). SPEM have been examined in this population, and while typically felt to be an important component of the visual complaints that are frequently voiced by individuals with persistent symptoms, studying this association has been met with equivocal results.[24] Given the importance of vision and the visual system to humans, the frequency of post-concussive symptoms that may be attributed to the visual system, suggestions of linkages in prior research and advances in eye tracking technology and analyses, further research into the use of techniques to study eye movements after mTBI is warranted.

This study examined the utility of a standardized eye tracking protocol to differentiate individuals with self-reported, chronic effects of mTBI from symptom-free individuals without a reported history of mTBI. For this investigation, we hypothesized that there would be significant injury-related differences in saccades, fixational, and SPEM eye movements between symptomatic individuals and controls. If present, these differential findings could be used to differentiate between individuals who have sustained an mTBI versus those who have not. Additionally, it is the first step in a potentially differentiate individuals with focused symptoms related to mTBI and those more likely due to other causes or co-morbid conditions.

Methods

This study received all appropriate institutional review board and governmental approvals. For this study, 60 subjects with PCS (Group A), who were part of a larger Department of Defense clinical trial, were recruited primarily from United States military bases and 26 normal controls (Group B) were recruited from an academic medical center. All subjects were evaluated by a TBI research team, led by a physiatrist (DXC), and a positive or negative history of TBI was ascertained. The diagnosis of TBI was confirmed by the study physiatrist's history, physical examination, and a review of any medical records for the subjects. Post-concussive symptoms, if present, were documented using the Rivermead Postconcussive Symptom Questionnaire (RPQ).[27]The RPQ is a widely used Likert-type symptom inventory consisting of 16 items [rated from 0 (never a problem) to 4 (severe problem)], designed to evaluate the somatic, cognitive and emotional functioning of individuals who have sustained a concussion. Whether part of the RPQ administration (subjects with mTBI) or via direct questioning, all subjects were questioned as to whether they had any subjective visual complaints, such as blurred vision, double vision, or floaters.

A head mounted video-based binocular eye tracker (Eyelink II, SR Research, Kanata, Ontario, CAN) was used to record horizontal and vertical binocular gaze data at 500 samples per second. To minimize head movement, the subject's head was supported by an adjustable chin rest cup. Stimuli covering ±20° horizontally and ±13° vertically were presented at 120 Hz on a 24-in LCD monitor placed 75 cm from the subject's eyes in a darkened room. The height of the monitor display was adjusted so that the center of the screen corresponded to the center of the pupillary plane. Calibration and validation of the eye tracker was performed at three points along

each cardinal axis immediately before recording commenced. The target stimulus was a white annulus, sized to occupy 0.25° of visual angle, with a high-contrast center point of 0.1° presented on a black background. Stimuli consisted of random, unpredictable step target movements and smooth pursuit paradigms in both the horizontal and vertical directions. Subjects were allowed to close their eyes and rest between each recording to prevent fatigue.

Eye position data were analyzed through a multi-step process involving initial visual inspection of the eye position recordings, followed by the use of specialized automated analysis algorithms, and lastly visual confirmation of the automated measures. In all trials, the horizontal and vertical positions of each eye were analyzed. During automated analysis, the criteria for detecting a saccade required that the amplitude of the movement was greater than ±0.1°, the duration of the saccade fell within a predetermined minimum and maximum time limit, and that the calculated velocity and acceleration values (based on a two-point central difference method) were greater than ±20°/s and ±400°/s^2, respectively, but also did not exceed a set of predetermined upper limits (in absolute value) for both velocity and acceleration. Responses that failed to meet the detection criteria for a saccade could then be considered as smooth pursuit, fixation when the eye is relatively stable, or artifact. If the response was considered artifact, the analysis program would identify and mark the data for further inspection. For any saccadic eye movement, the time, location, and amplitude of the saccade, as well as, its direction, duration, peak velocity, and peak acceleration and deceleration reached during the movement were determined and stored in a measurement summary file for later statistical analysis. For trials involving step changes in target position, the response latency (the time between the onset of target movement and response) were measured and recorded. The saccadic gain was calculated as the ratio between the amplitude of the primary saccade (first saccade after target movement)

and the displaced target amplitude (total change in target position). As a measure of positioning accuracy, the number and amplitudes of any additional corrective saccades that occurred after the primary saccade were recorded, as well as the final position error between the target and the eye. The inter-saccadic interval (time between saccades) defined a period the affixation period, or potentially, the duration of smooth pursuit.

Fixation is characterized by relatively stable eye position with movement that has low velocity, low acceleration and no directional trend. During fixation, the length of time was recorded and several measures of stability were performed. Stability measures included computation of the position variance, computation of the root mean square (RMS) of eye velocity, and determination of the mean and absolute mean velocity of the eyes during fixation. As an additional measure of stability, bivariate contour elliptical analysis (BCEA) was used to define the orientation, semi-major and semi-minor dimensions, and area ($degs^2$) of an elliptical contour which captured 90 percent of the fixation data during fixation on the zero degree, center target position. These same data were also applied to a discrete Fourier transform (DFT) which determiner the frequency content or spectrum during fixation.

Smooth pursuit occurs when the velocity of the eye closely matches the direction and velocity of the target. Velocity mismatches between eye and target result in position errors, which are corrected by saccadic intrusions. During pursuit, the velocity of the eye is greater compared to fixation velocity, while the pursuit acceleration is far less than what occurs during a saccade. During periods of smooth pursuit, the number of saccades, saccadic amplitude, and pursuit gain were determined. Pursuit gain, defined as the ratio between the weighted mean eye velocity and target velocity, was determined without inclusion of any corrective saccades.

Results

Statistical Analyses. All statistical analyses were conducted using SPSS Statistics version 21.0 (IBM SPSS). Data were assessed for normality using the Shapiro-Wilk test. Parameters that were not normally distributed (i.e., Shapiro-Wilk P value>.05) were then log-transformed and rechecked for normality. Independent-sample, unpaired, 2-tailed t-tests (on either original variables or log transformed variables) were conducted to assess for differences between Groups A and B. The Levene test for the equality of variances was calculated, and if the significance was found to be less than .05, equal variances were not assumed. In many cases, the data did not give any indication that the populations were normal or even log-normal (predominantly because of outliers). For these variables, we used the non-parametric Mann-Whitney U test for comparing independent samples. For each task, data from the right eye were analyzed as no within group left-right eye differences were noted in the cohort. Given the challenges in normalizing all data, the number of subject measurement points varied from task to task.

Descriptive Data. There were 60 research subjects with symptomatic mTBI (Group A) and 26 control subjects without a history of TBI or symptoms (Group B). All Group A subjects were male and had a mean age of 23.2 years (SD=2.95). Two (3.0%) were African-American, 47 (78.3%) were Caucasian, 10 (16.6%) were Hispanic, and one (1.6%) was Native American. All 60 had experienced at least one mTBI, with the most recent TBI occurring a mean of 8.5 months (SD= 6.58 months, range= 3-39 months) prior to the baseline assessments. Cause of concussion included improvised explosive device (IED) blast (85.3%), rocket propelled grenades (3.0%), and mortar attacks (1.7%). The remaining 10% were uncategorized blasts. Slightly more than one-quarter of the participants self-reported additional concussions (M = 2.1, SD=.95, range=1-

4) prior to the most recent blast injury. The symptoms of the Group A cohort were characterized as mild on the RPQ symptomatic, with 7 of the 16 items endorsed in the range of 2 (a mild problem) and only one item (forgetfulness) in the range of 3 (a moderate problem).13 Importantly, the three vision-related items, blurred vision, light sensitivity and double vision, on the RPQ were reported as either never having been a problem or no longer a problem, so no subjects reported active difficulty with vision. Twenty six healthy undergraduate, graduate or post-graduate trainees served as controls. None had sustained a mild TBI and all were asymptomatic.

Saccades. Saccadic data from the horizontal and vertical target displacement tasks for subjects with symptomatic mTBI and controls were compared using 11 measures (see Table 1). Data from horizontal and vertical direction eye movements were analyzed for the horizontal and vertical target displacement tasks, respectively.

*** Insert Table 1 Here ***

Main Sequence Data for Saccadic Data. For each subject, peak velocity, peak acceleration, duration and saccadic amplitude data for all saccades were fit to the models for both horizontal and vertical displacement tasks. All fits were performed using the nonlinear curve fitting toolbox in MATLAB (Mathworks, MA). As is standard in the eye-tracking literature, exponential models were used for peak velocity and peak acceleration, while a power function model was used for duration.[28] This process generated the parameters asymptotic velocity, asymptotic acceleration, exponential rise (for both velocity and acceleration), predicted duration

of a 1 degree saccade, and the percentage rate of change for predicted duration of a 1-degree saccade, giving rise to 6 measures. The root-mean-square error for each of the three model fits was checked for goodness of fit. The RMSE was also compared between groups to see if one group had more variance than the other, adding 3 more measures. After curves were fit for each subject, the predicted peak velocity, peak acceleration, and duration from the models for 1 degree and 5 degree saccades were compared between symptomatic mTBI subjects and controls, providing 5 more measures. Figure 1 shows typical model fits for peak velocity, acceleration and duration.

*** Insert Figure 1 Here ***

Horizontal and Vertical Tracking Step Data. Of the 11 accuracy variables and the 14 main sequence variables, 11 (5 accuracy and 6 main sequence) variables show significant differences between Groups A and B for both horizontal and vertical displacement tasks (p-value < .05). Results are summarized in Tables 2 and 3.

*** Insert Tables 2 and 3 Here ***

Smooth Pursuit. Data for horizontal and vertical smooth pursuit tasks were analyzed using 7 measures (see Table 4). Data from eye movement in the horizontal and vertical directions were analyzed for the horizontal and vertical smooth pursuit tasks, respectively.

*** Insert Table 4 Here ***

Horizontal and Vertical Ramp Data. Of these seven variables, only two showed significant differences between Groups A and B (p-value < .05). No support was present in any of the cases for an assumption that data came from a normally distributed population even after log transformation. Accordingly, in our analysis, the non-parametric Mann-Whitney U test for comparing independent samples was used.

*** Insert Table 5 Here ***

Fixation. Fixation data for all subjects came from fixations between saccades from the horizontal target displacement task. To minimize the potential effect due to target eccentricity, only fixations around the origin were included in the analysis. Fixation was compared between groups using 10 measures (see Table 6).

*** Insert Table 6 Here ***

No differences were found using either parametric or non-parametric methods. Additionally, no results were found running parametric tests on log transformed data, which was closer to normally distributed.

Discussion

Diagnosing and monitoring recovery after mTBI, using either subjective or objective parameters, is challenging. Importantly, the study revealed significant differences in a number of eye

tracking components, both for tasks involving a step displacement of the target and for smooth pursuit tasks. Uncovering these differences represents a vital initial step towards development of objective tests which can discriminate between individuals with symptomatic mTBI and controls. This investigation represents the first examination of the utility of eye tracking to identify objective findings in individuals with subjective symptoms after mTBI using a non-mTBI control group for comparison. Given the challenges of both diagnosing and monitoring recovery after mTBI, using either subjective or objective parameters, this study represents a significant step forward.

Importantly, we found significant differences in two of the three eye tracking parameters studied: saccades and SPEM. Robust differences were found between responses of subjects with symptomatic mTBI and controls to horizontal and vertical stepwise target displacement tasks, with subjects with symptomatic mTBI having statistically larger position errors, smaller saccadic amplitudes, smaller predicted peak velocities, smaller peak accelerations, and longer durations. Subjects with symptomatic mTBI were also more likely to respond to step changes in target position with smaller primary saccades compared to controls. In general, symptomatic mTBI tracked the stepwise moving targets less accurately, revealing possible brain dysfunction. This investigation represents the first examination of the utility of eye tracking using a non-mTBI control group as a means to identify objective findings in individuals with subjective symptoms after mTBI. Differences in responses to smooth pursuit tasks were also found between subject groups, although not as robust as the differences between mTBI subjects and controls. Here, the saccadic amplitudes were significantly different. The amplitudes were larger for subjects with symptomatic mTBI for the horizontal smooth pursuit task. In comparison to controls, pursuit gain was lower among subjects with symptomatic mTBI. Surprisingly, in contrast to a number of

other neurological disorders, no differences were found between groups for fixation measures. Further investigation into the specificity and sensitivity of these measures in light of the often complex polytraumatic nature of individuals with either combat or civilian-related injury (e.g., presence of acute or chronic conditions, anxiety disorders, depression, pain and substance abuse) is warranted. This represents an important initial step in the understanding of the role of both eye movement abnormalities and computerized eye tracking in the diagnosis and monitoring of symptomatic mTBI. Specific linkages between symptoms, eye tracking abnormalities, and neuropathology (as revealed by neuroimaging) may be an important subsequent step.

The wide array of abnormalities uniquely found in the mTBI cohort may have contributed to their diverse complaints, including headache, blurred/double vision, dizziness, clumsiness, reading difficulties, and driving problems. Future studies correlating the magnitude and type of the range of eye movement errors with ecologic complaints would be a fruitful area of further investigation. These analyses could also assist in the development of both predictive models for symptom development and recovery, and in the development of effective treatments for specific symptom-eye tracking abnormality associations.

This study utilized standard protocols to define exposure to a PCE, to be symptomatic for PCS, and for eye tracking, which allowed us to remove much of the subjectively commonly encountered in mTBI research. However there were some limitations to the research design that may limit its generalizability. These include; gender, restricted age, etiology of mTBI, chronicity of mTBI and symptoms, variability in symptom treatments, and co-morbid conditions. These restrictions may be less significant, in particular to the Departments of Defense and Veterans Affairs systems, since the bulk of individuals with mTBI seen in these systems tend to be younger males with complex military theatre polytrauma injuries.[29] Future studies will focus on

larger samples of individuals that include cohorts with more discrete causes of symptom complex (e.g., isolated mTBI, isolated stress disorders, isolated pain complaints), in an attempt to identify unique patterns of eye movement abnormalities based on etiology of symptoms. Additionally, analyses of the impact of symptom patterns on eye movement seen, as well as the association between differential patterns of eye movement abnormalities with symptom presentations, can be performed with larger subject samples. Lastly, temporal associations between injury, symptom presentation, and eye movement abnormalities may be an important key to use of eye tracking to monitor recovery after mTBI.

References

1. http://newsfeed.time.com/2013/06/19/head-trauma-sensors-aim-to-measure-concussion-risks/; http://www.thedailybeast.com/newsweek/2010/11/08/

2. http://www.thedailybeast.com/newsweek/2010/11/08/veteran-s-head-injuries-confound-military-doctors.html

3. http://www.healthquality.va.gov/Rehabilitation_of_Concussion_mTBI.asp

4. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. *N Engl J Med* 2008; 358:453-463.

5. Brenner LA, Vanderploeg RD,Terrio H. Assessment and diagnosis of mild traumatic brain injury, posttraumatic stress disorder, and other polytrauma conditions: Burden of adversity hypothesis. *Rehabil Psych* 2009;54(3):239-246.

6. ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010, F07.2 Postconcussional syndrome, World Health Organization.

7. Arciniegas DB, Topkoff JL. Applications of the P50 evoked response to the evaluation of cognitive impairments after traumatic brain injury. *Phys Med Rehabil Clin N Am* 2004 Feb;15(1):177-203.

8. Gosselin N, Bottari C, Chen JK, Petrides M, Tinawi S, de Guise E, Ptito A. Electrophysiology and functional MRI in post-acute mild traumatic brain injury. *J Neurotrauma* 2011;28(3):329-41.

9. Nuwer MR, Hovda DA, Schrader LM, Vespa PM Routine and quantitative EEG in mild traumatic brain injury. *Clin Neurophysiol* 2005;116(9):2001-25.

10. Cohen BA, Inglese M, Rusinek H, Babb JS, Grossman RI, Gonena O. MR Spectroscopy and MRI-Volumetry in Mild Traumatic Brain Injury. *AJNR* 2007;28:907-913.

11. McAllister TW, Saykin AJ, Flashman LA, Sparling MB, Johnson SC, Guerin SJ, Mamourian AC, Weaver JB, Yanofsky N. Brain activation during working memory 1 month after mild traumatic brain injury: a functional MRI study. *Neurol* 1999;53(6):1300-8.

12. Yuh EL, Mukherjee P, Lingsma HF, Yue JK, Ferguson AR, Gordon WA, Valadka AB, Schnyer DM, Okonkwo DO, Maas AI, Manley GT; TRACK-TBI Investigators. Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. *Ann Neurol* 2013 Feb;73(2):224-35.

13. Buxton RB, Uludağ K, Dubowitz DJ, Liu TT. Modeling the hemodynamic response to brain activation. *Neuroimage* 2004;23 Suppl 1:S220-33.

14. Deppe M, Ringelstein EB, Knecht S. The investigation of functional brain lateralization by transcranial Doppler sonography. *Neuroimage* 2004;21(3):1124-46.

15. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation *Br J Anaesth* 2009;103 (suppl 1): i3-i13.

16. Pickett TC, Radfar-Baublitz LS, McDonald SD, Walker WC, Cifu DX. Objectively assessing balance deficits after TBI: Role of computerized posturography. *J Rehabil Res Dev* 2007;44(7):983-90.

17. Guskiewicz KM, Ross SE, Marshall SW. Postural Stability and Neuropsychological Deficits After Concussion in Collegiate Athletes. J Athl Train 2001;36(3):263-273.

18. Brenner LA, Terrio H, Homaifar BY, Gutierrez PM, Staves PJ, Harwood JE, Reeves D, Adler LE, Ivins BJ, Helmick K, Warden DF. Neuropsychological test performance in soldiers with blast-related mild TBI. *Neuropsychol* 2010;24(2):160-7.

19. Ceranic B, Prasher D, Raglan E, Luxon L. Tinnitus after head injury: evidence from otoacoustic emissions *J Neurol Neurosurg Psychiatry* 1998; 65(4): 523–529

20. http://www.dcoe.health.mil/Content/navigation/documents/Portable%20Field-Based%20Devices%20for%20the%20Early%20Diagnosis%20of%20mTBI.pdf

21. Kraus MF, Little DM, Donnell AJ, Reilly JL, Simonian N, Sweeney JA. Oculomotor Function in Chronic Traumatic Brain Injury. *Cog Behav Neurol*. 2007; 20(3): 170-178. PMID:17846516

22. Heitger MH, Jones RD, Anderson TJ. A new approach to predicting postconcussion syndrome after mild traumatic brain injury based upon eye movement function. *Conf Proc IEEE Eng Med Biol Soc*. 2008; 2008:3570-3. doi: 10.1109/IEMBS.2008.4649977

23. Ciuffreda, LLudlam D, Thiagarajan P. Oculomotor diagnostic protocol for the mTBI population. *Optometry*. 2011; 82(2): 61-63. doi: 10.1016/j.optm.2010.11.011.

24. Ramat S, Leigh RJ, Optican LM. What clinical disorders tell us about the neural control of saccadic eye movements. *Brain*. 2007; 130: 10-35. doi: 10.1093/brain/awl309.

25. Suh M, Kolster R, Sarkar R, McCandliss B, Ghajar J, Cognitive and Neurobiological Research Consortium. Deficits in predictive smooth pursuit after mild traumatic brain injury. *Neurosci Lett.* 2006; 401(1-2): 108-113. doi: 10.1016/j.neulet.2006.02.074.

26. Cifu DX, Hart BB, West SL, Walker WC, et al. The effect of hyperbaric oxygen on persistent post-concussive symptoms. J Head Trauma Rehabil. doi: 10.1097/HTR.0b013e3182a6aaf0

27. Eyres S, Carey, A, Gilworth, G., Neumann V, Tennant, A. Construct validity and reliability of the Rivermead post-concussion symptoms questionnaire. Clinical Rehabil 2005 19(8), 878-887

28. Leigh, R. John, Zee, David S. The Neurology of Eye Movements, Oxford University Press:2006.

29. Cifu DX, Blake P: Overcoming Post-Deployment Syndrome: A Six-Step Mission to Health. DemosHealth, New York, 2011.

Table 1
Measures for Comparing Saccadic Data

Number of Primary Saccades: the number of times the subject made at least one saccadic movement following a target movement (if target moved again before the subject then no primary saccade was recorded)
Number of correcting saccades: the total number of saccades excluding the primary saccades following the target movements
Average Latency: the mean reaction time to each target movement
Primary Position Error: the absolute value of the difference between the target displacement and the amplitude of the primary saccades. Three sub-measures of primary position error were calculated: • **Mean of the Normalized Position Error.** the mean of the absolute value of the ratio between the position error and the target amplitude. Normalization attempts to account for the dependency of the amplitude of the position error on the amplitude of the target displacement. • **Standard Deviation of the Ratios of the Position Error and the Target Displacement.** • **Mean of the Absolute Value of the Non-normalized Position Errors.**
Final Position Error: the absolute value of the difference between the target displacement and the position of the eye before the next target movement. The same three sub-measures for primary position error were calculated for final position error.
Mean of the Absolute Value of the Normalized Primary Saccadic Amplitude: the mean of the absolute value of the ratio between the primary saccadic amplitude and the target amplitude for all saccades per individual. Here, normalization attempts to account for the dependency of the amplitude of the primary saccades on the amplitude of the target displacement.
Mean Q-Ratio: the mean of the ratio between peak velocity and saccadic amplitude over all saccades per individual.

Table 2
Horizontal Displacement Task

HORIZONTAL TRACKING	**Mean Group A**	**Mean Group B (control)**	**Significance Level**	**Type of test***
Mean of normalized primary position error	.4255	.2043	.000	nonparametric
SD of normalized primary position error	.6993	.3502	.000	nonparametric
Mean of normalized final position error	.2993	.1346	.016	nonparametric
Mean of non-normalized primary position error	4.7572	2.3803	.000	nonparametric
Number of primary saccades	20.64	24.92	.000	nonparametric
Predicted Velocity, 1-deg amp	55.4612	59.4678	.008	parametric
Predicted Velocity, 5-deg amp	219.71	235.51	.001	parametric
Predicted Acceleration, 1-deg amp	3464.97	3712.18	.026	parametric
Predicted Acceleration, 5-deg amp	12495.4	13530.74	.003	parametric
Predicted Duration, 1-deg amp	36.60	34.71	.000	nonparametric
Predicted Duration, 5-deg amp	61.62	56.93	.000	nonparametric

CAPTION: 55 Group A and 26 Group B had complete results for all of the horizontal target displacement tasks

*In all cases in this table, the employment of nonparametric rather than parametric tests did not affect whether the difference between groups was significant.

Table 3
Vertical Displacement Task

VERTICAL TRACKING	**Mean Group A**	**Mean Group B (control)**	**Significance Level**	**Type of test***
Mean of normalized primary position error	.4093	.2523	.002	parametric
SD of normalized primary position error	.5737	.3416	.011	nonparametric
Mean of normalized final position error	.3184	.1817	.004	parametric
Mean of non-normalized primary position error	3.0513	1.9616	.054*	parametric
Number of primary saccades	22.74	24.72	.000	nonparametric
Predicted Velocity, 1-deg amp	52.61	58.94	.000	parametric
Predicted Velocity, 5-deg amp	213.5	229.9	.001	parametric
Predicted Acceleration, 1-deg amp	3121.93	3508.92	.000	parametric
Predicted Acceleration, 5-deg amp	11714.6	12906.8	.000	nonparametric
Predicted Duration, 1-deg amp	39.36	35.97	.000	parametric
Predicted Duration, 5-deg amp	66.67	59.78	.000	nonparametric

CAPTION: 47 Group A and 26 Group B had complete results for all of the vertical target displacement tasks.

*In all cases in this table, the employment of nonparametric rather than parametric tests did not affect whether the difference between groups was significant.

Table 4
Measures for Comparing Smooth Pursuit Data

Number of Saccades: the total number of saccades during a smooth pursuit task
Mean Gain: the mean of the ratios of eye velocity and target velocity between saccades
Minimum Gain: the minimum of the ratios of eye velocity and target velocity between saccades
Maximum Gain: the maximum of the ratios of eye velocity and target velocity between saccades
Mean Absolute Saccadic Amplitude: the mean of the absolute value of saccadic amplitude calculated across all saccades during the tasks
Mean Duration: the mean length of time eyes are smoothly pursuing the target between saccades
Mean Absolute Normalized Saccadic Amplitude: the mean of the absolute value of the ratio of saccadic amplitude and target velocity. Normalization by target velocity attempts to account for dependency of saccadic amplitude on the velocity of the target.

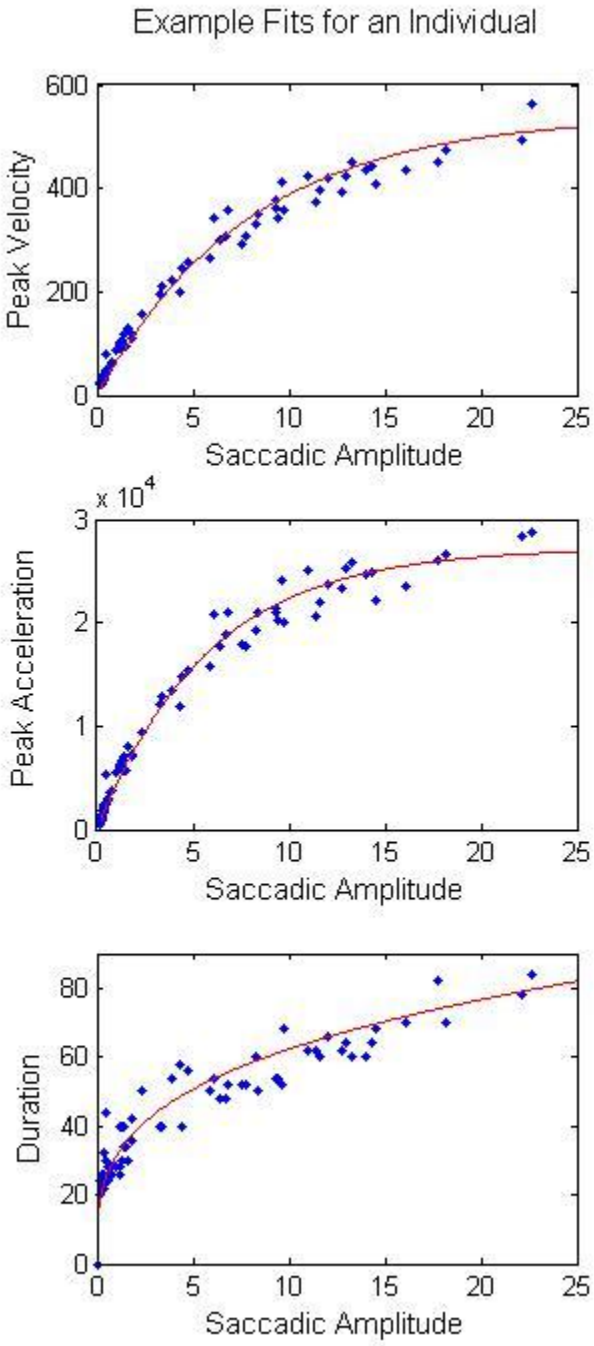
Table 5
Smooth Pursuit Ramp Data

HORIZONTAL RAMP	Mean Group A	Mean Group B (control)	Significance Level
Min Gain	.0804	.1088	.000
Mean normalized amplitude	.2208	.1561	.017

VERTICAL RAMP	Mean Group A	Mean Group B (control)	Significance Level
Min Gain	.0761	.1013	.011
Mean normalized amplitude	.2253	.2933	.016

CAPTION: 55 Group A and 24 Group B had complete results for all of the horizontal smooth pursuit tasks; 49 Group A and 23 Group B had complete results for all of the vertical smooth pursuit tasks

Figure 1
Sample Model Fits



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Caption: Example model fits for an individual subject. Peak Velocity, Acceleration and Duration versus Saccadic Amplitude (Top, Middle and Bottom, respectively). The blue dots represent absolute values of data recorded from a horizontal step displacement task. The red lines are the corresponding model fits.

Table 1
Measures for Comparing Saccadic Data

Number of Primary Saccades: the number of times the subject made at least one saccadic movement following a target movement (if target moved again before the subject then no primary saccade was recorded)
Number of correcting saccades: the total number of saccades excluding the primary saccades following the target movements
Average Latency: the mean reaction time to each target movement
Primary Position Error: the absolute value of the difference between the target displacement and the amplitude of the primary saccades. Three sub-measures of primary position error were calculated: • **Mean of the Normalized Position Error.** the mean of the absolute value of the ratio between the position error and the target amplitude. Normalization attempts to account for the dependency of the amplitude of the position error on the amplitude of the target displacement. • **Standard Deviation of the Ratios of the Position Error and the Target Displacement.** • **Mean of the Absolute Value of the Non-normalized Position Errors.**
Final Position Error: the absolute value of the difference between the target displacement and the position of the eye before the next target movement. The same three sub-measures for primary position error were calculated for final position error.
Mean of the Absolute Value of the Normalized Primary Saccadic Amplitude: the mean of the absolute value of the ratio between the primary saccadic amplitude and the target amplitude for all saccades per individual. Here, normalization attempts to account for the dependency of the amplitude of the primary saccades on the amplitude of the target displacement.
Mean Q-Ratio: the mean of the ratio between peak velocity and saccadic amplitude over all saccades per individual.

Table

Table 2
Horizontal Displacement Task

HORIZONTAL TRACKING	**Mean Group A**	**Mean Group B (control)**	**Significance Level**	**Type of test***
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Std dev of normalized primary position error	.6993	.3502	.000	nonparametric
Mean of normalized final position error	.2993	.1346	.016	nonparametric
Mean of non-normalized primary position error	4.7572	2.3803	.000	nonparametric
Number of primary saccades	20.64	24.92	.000	nonparametric
Predicted Velocity, 1-deg amp	55.4612	59.4678	.008	parametric
Predicted Velocity, 5-deg amp	5.3852	5.4592	.001	parametric
Predicted Acceleration, 1-deg amp	3464.97	3712.18	.026	parametric
Predicted Acceleration, 5-deg amp	12495.4	13530.74	.003	parametric
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CAPTION: 47 Group A and 26 Group B had complete results for all of the vertical target displacement tasks.

*****In all cases in this table, the employment of nonparametric rather than parametric tests did not affect whether the difference between groups was significant.

Table

Table 4
Measures for Comparing Smooth Pursuit Data

Number of Saccades: the total number of saccades during a smooth pursuit task
Mean Gain: the mean of the ratios of eye velocity and target velocity between saccades
Minimum Gain: the minimum of the ratios of eye velocity and target velocity between saccades
Maximum Gain: the maximum of the ratios of eye velocity and target velocity between saccades
Mean Absolute Saccadic Amplitude: the mean of the absolute value of saccadic amplitude calculated across all saccades during the tasks
Mean Duration: the mean length of time eyes are smoothly pursuing the target between saccades
Mean Absolute Normalized Saccadic Amplitude: the mean of the absolute value of the ratio of saccadic amplitude and target velocity. Normalization by target velocity attempts to account for dependency of saccadic amplitude on the velocity of the target.

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Table 5
Smooth Pursuit Ramp Data

HORIZONTAL RAMP	Mean Group A	Mean Group B (control)	Significance Level
Min Gain	.0804	.1088	.000
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VERTICAL RAMP	Mean Group A	Mean Group B (control)	Significance Level
Min Gain	.0761	.1013	.011
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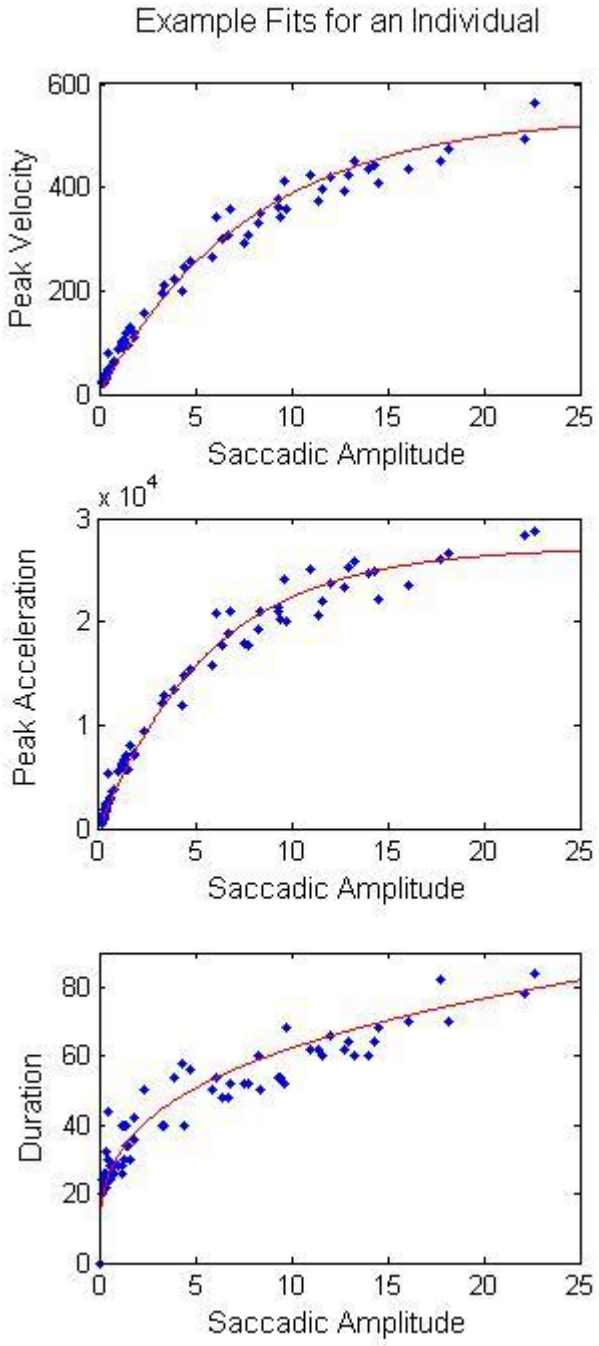
Figure 1
Sample Model Fits



Caption: Example model fits for an individual subject. Peak Velocity, Acceleration and Duration versus Saccadic Amplitude (Top, Middle and Bottom, respectively). The blue dots represent absolute values of data recorded from a horizontal step displacement task. The red lines are the corresponding model fit.

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Differential Eye Movements in Mild Traumatic Brain Injury vs. Normal Controls

Abstract

Objective measures to diagnose and to monitor improvement of symptoms following mild traumatic brain injury (mTBI) are lacking. Computerized eye tracking has been advocated as a rapid, user friendly and field ready technique to meet this need. Eye tracking data collected via a head mounted, video-based binocular eye tracker was used to examine saccades, fixations and smooth pursuit movement in 60 military Service Members with post concussive syndrome (PCS) and 26 asymptomatic control subjects in an effort to determine if eye movement differences could be found and quantified. The diagnosis of mTBI was confirmed by the study physiatrist's history, physical examination, and a review of any medical records. Results demonstrated that subjects with symptomatic mTBI had statistically larger position errors, smaller saccadic amplitudes, smaller predicted peak velocities, smaller peak accelerations, and longer durations. Subjects with symptomatic mTBI were also less likely to follow a target movement (less primary saccades). In general, symptomatic mTBI tracked the stepwise moving targets less accurately, revealing possible brain dysfunction. A reliable, standardized protocol that appears to differentiate mTBI from normals was developed for use in future research. This investigation represents a step toward objective identification of those with PCS. Future studies focused on increasing the specificity of eye movement differences in those with PCS are needed.

Key words: mild traumatic brain injury, post-concussion syndrome, eye tracking, saccades, fixations, smooth pursuit

Introduction

As a result of injuries to both military servicemembers in combat and athletes in contact sports, there has been heightened focus on metrics to diagnose and monitor recovery after mild traumatic brain injury (mTBI) and related sequelae.[1,2] A significant limiting factor in the diagnostic approach to mTBI has been the dependence on self-report of injury and symptoms, resulting in a provisional syndromic-based diagnosis, post-concussion syndrome (PCS). Increasingly there has been recognition that an mTBI is more accurately termed as a "potentially concussive event" (PCE), rather than a syndrome.[3-5] If specific criteria (e.g., alteration or loss of consciousness with associated memory loss/amnesia surrounding the event) are confirmed, then the diagnosis of mTBI may be made. If these criteria are not met, then the PCE cannot be labeled as an mTBI, but may still manifest with symptoms related to secondary physical injury (e.g., neck or skull-based musculature and other soft-tissue) and psychological trauma (e.g., acute stress reaction). It is more proper to apply the "syndrome" label only after the mTBI has been confirmed and has manifest in a symptom complex that has persisted for more than three months after injury.[6] Importantly, even in the case of a confirmed mTBI, the effects of other physical and psychological conditions often contribute to the symptoms and syndrome.[5]

The limitations of the current self-reported, subjective accounting of traumatic events, symptoms, and improvements are manifold. Without objective documentation of the PCE, such as pre-event neuropsychological screening, event videotaping, or data from accelerometers, these potential confounders include: altered or imprecise recall of event duration, severity, and date of occurrence, potentially inaccurate estimation of pre-event functioning, impact of acute stress response, and motivation (positive or negative) to accurately report symptoms. These factors are further influenced by the elapsed time between the event and medical assessment of the subject.

This is important at both the proximal (e.g., secondary factors surrounding the event or trauma that resulted in the PCE, acute recognition of PCE and/or mTBI, acute management of PCE/mTBI) and distal (e.g., increasing inaccuracy of precise recall weeks, months, or even years post-event, subsequent symptoms that arise after PCE, recognition, acknowledgement, and eventual assessment of the PCE/mTBI, ongoing management of the PCE and subsequent symptoms) ends of the encounter with the medical professional.

In addition to the use of self-reported injury events and post-injury symptoms, cognitive screens and more comprehensive neuropsychological testing have predominantly been utilized to diagnose and monitor recovery after mTBI. While this approach is well validated and has proven clinically useful, it also has a number of inherent limitations. Principal criticisms of the testing approach include the subjectivity of self-report, patient fatigue and motivation factors, practice effects, and influence of co-morbid conditions (e.g., pain, anxiety, depression, substance abuse). Additionally, testing batteries often vary in composition based on the practice patterns of individual clinicians, limiting the ability to compare across time and testing centers, with subsequent limitations on meaningful meta-analysis. There is no universally accepted neuropsychological testing battery after PCE.

There is increasing enthusiasm to rely on objective measures to determine the relationship of both a PCE to an mTBI and an mTBI to persistent symptoms. There are few well-designed, large scale studies examining early brain changes following mTBI using diagnostic devices, although many devices and techniques for objectively measuring the brain have been proposed and examined. Some involve measures of brain activity (e.g., electroencephalography [EEG], evoked responses)[7-9], structure (diffusion tensor imaging [DTI], high density fiber tracking [HDFT])[10-12], hemodynamics (e.g., near-infrared spectroscopy [NIRS], transcranial

Doppler ultrasound [TCD])[13-15], and functional testing (e.g., computerized posturography, computerized tests of cognition and executive function)[16-18]. Other efforts have focused on devices that attempt to measure intracranial pathology, such as intracranial hypertension via observation of extracranial phenomena (e.g., optic nerve sheath diameter [ONSD] or otoacoustic emissions).[19] Despite the vigor of studying the utility and validity of these diagnostic approaches, none have achieved a level of efficacy to be considered as the "gold standard," and multidimensional approaches using diagnostic algorithms have not been developed.

One method for the objective assessment of the brain after PCE and mTBI that has shown promise as a user friendly, low cost, non-invasive, definitive approach is eye tracking. Eye tracking has been advocated as a rapid, convenient, and portable (i.e., field ready) method of evaluation However, specific research on its specificity and sensitivity is sparse in this population. Although specific values are not universally presented,[20] one study suggested that the sensitivity and specificity of eye tracking paradigms reaches 100% when differentiating controls from mTBI, or even differentiating PCS from non-PCS in a suspected mTBI population.[21] These results have not been replicated. Previous reports have shown the primary oculomotor deficits in mTBI to be difficulty reading (oculomotor specific), vergence, accommodation, and saccadic gain abnormalities.[22] Eye tracking assessment typically involves the examination of saccades, fixation, and smooth pursuit eye movements (SPEM). Saccades (rapid, accurate, ballistic shifting of gaze to a new area of interest) are studied because they require the complex coordination and timing of neural circuitry in numerous different brain areas, including primarily the frontal lobe, basal ganglia, superior colliculus, and the cerebellum; and would therefore be likely to be sensitive indicators of injury to one of these areas.[23] Further, the various parameters (e.g. direction, gain, velocity, trajectory, etc.) of saccades are "programmed" independent of each

other, generally free of cognitive influence, and can be studied both separately and in combination.[23] Up to the present, fixation (maintaining an image of interest on the fovea) data have not been well studied in TBI patients, largely due to the technical challenges in measuring fixations, and the prevailing belief that the fixations themselves are "silent," offering no meaningful data. Fortunately, the technological limitations have been largely overcome with the latest generation of measurement tools and applied analyses. The "silent" nature of fixation deficits seems likely more an under appreciation of the linkage between subtle (often difficult to measure) visual processing deficits and a range of functional tasks (e.g., reading, driving) or somatic complaints (e.g., headache, dizziness). SPEM have been examined in this population, and while typically felt to be an important component of the visual complaints that are frequently voiced by individuals with persistent symptoms, studying this association has been met with equivocal results.[24] Given the importance of vision and the visual system to humans, the frequency of post-concussive symptoms that may be attributed to the visual system, suggestions of linkages in prior research and advances in eye tracking technology and analyses, further research into the use of techniques to study eye movements after mTBI is warranted.

This study examined the utility of a standardized eye tracking protocol to differentiate individuals with self-reported, chronic effects of mTBI from symptom-free individuals without a reported history of mTBI. For this investigation, we hypothesized that there would be significant injury-related differences in saccades, fixational, and SPEM eye movements between symptomatic individuals and controls. If present, these differential findings could be used to differentiate between individuals who have sustained an mTBI versus those who have not. Additionally, it is the first step in a potentially differentiate individuals with focused symptoms related to mTBI and those more likely due to other causes or co-morbid conditions.

Methods

This study received all appropriate institutional review board and governmental approvals. For this study, 60 subjects with PCS (Group A), who were part of a larger Department of Defense clinical trial, were recruited primarily from United States military bases and 26 normal controls (Group B) were recruited from an academic medical center. All subjects were evaluated by a TBI research team, led by a physiatrist (DXC), and a positive or negative history of TBI was ascertained. The diagnosis of TBI was confirmed by the study physiatrist's history, physical examination, and a review of any medical records for the subjects. Post-concussive symptoms, if present, were documented using the Rivermead Postconcussive Symptom Questionnaire (RPQ).[27]The RPQ is a widely used Likert-type symptom inventory consisting of 16 items [rated from 0 (never a problem) to 4 (severe problem)], designed to evaluate the somatic, cognitive and emotional functioning of individuals who have sustained a concussion. Whether part of the RPQ administration (subjects with mTBI) or via direct questioning, all subjects were questioned as to whether they had any subjective visual complaints, such as blurred vision, double vision, or floaters.

A head mounted video-based binocular eye tracker (Eyelink II, SR Research, Kanata, Ontario, CAN) was used to record horizontal and vertical binocular gaze data at 500 samples per second. To minimize head movement, the subject's head was supported by an adjustable chin rest cup. Stimuli covering ±20° horizontally and ±13° vertically were presented at 120 Hz on a 24-in LCD monitor placed 75 cm from the subject's eyes in a darkened room. The height of the monitor display was adjusted so that the center of the screen corresponded to the center of the pupillary plane. Calibration and validation of the eye tracker was performed at three points along

each cardinal axis immediately before recording commenced. The target stimulus was a white annulus, sized to occupy 0.25° of visual angle, with a high-contrast center point of 0.1° presented on a black background. Stimuli consisted of random, unpredictable step target movements and smooth pursuit paradigms in both the horizontal and vertical directions. Subjects were allowed to close their eyes and rest between each recording to prevent fatigue.

Eye position data were analyzed through a multi-step process involving initial visual inspection of the eye position recordings, followed by the use of specialized automated analysis algorithms, and lastly visual confirmation of the automated measures. In all trials, the horizontal and vertical positions of each eye were analyzed. During automated analysis, the criteria for detecting a saccade required that the amplitude of the movement was greater than ±0.1°, the duration of the saccade fell within a predetermined minimum and maximum time limit, and that the calculated velocity and acceleration values (based on a two-point central difference method) were greater than ±20°/s and ±400°/s^2, respectively, but also did not exceed a set of predetermined upper limits (in absolute value) for both velocity and acceleration. Responses that failed to meet the detection criteria for a saccade could then be considered as smooth pursuit, fixation when the eye is relatively stable, or artifact. If the response was considered artifact, the analysis program would identify and mark the data for further inspection. For any saccadic eye movement, the time, location, and amplitude of the saccade, as well as, its direction, duration, peak velocity, and peak acceleration and deceleration reached during the movement were determined and stored in a measurement summary file for later statistical analysis. For trials involving step changes in target position, the response latency (the time between the onset of target movement and response) were measured and recorded. The saccadic gain was calculated as the ratio between the amplitude of the primary saccade (first saccade after target movement)

and the displaced target amplitude (total change in target position). As a measure of positioning accuracy, the number and amplitudes of any additional corrective saccades that occurred after the primary saccade were recorded, as well as the final position error between the target and the eye. The inter-saccadic interval (time between saccades) defined a period the affixation period, or potentially, the duration of smooth pursuit.

Fixation is characterized by relatively stable eye position with movement that has low velocity, low acceleration and no directional trend. During fixation, the length of time was recorded and several measures of stability were performed. Stability measures included computation of the position variance, computation of the root mean square (RMS) of eye velocity, and determination of the mean and absolute mean velocity of the eyes during fixation. As an additional measure of stability, bivariate contour elliptical analysis (BCEA) was used to define the orientation, semi-major and semi-minor dimensions, and area ($degs^2$) of an elliptical contour which captured 90 percent of the fixation data during fixation on the zero degree, center target position. These same data were also applied to a discrete Fourier transform (DFT) which determiner the frequency content or spectrum during fixation.

Smooth pursuit occurs when the velocity of the eye closely matches the direction and velocity of the target. Velocity mismatches between eye and target result in position errors, which are corrected by saccadic intrusions. During pursuit, the velocity of the eye is greater compared to fixation velocity, while the pursuit acceleration is far less than what occurs during a saccade. During periods of smooth pursuit, the number of saccades, saccadic amplitude, and pursuit gain were determined. Pursuit gain, defined as the ratio between the weighted mean eye velocity and target velocity, was determined without inclusion of any corrective saccades.

Results

Statistical Analyses. All statistical analyses were conducted using SPSS Statistics version 21.0 (IBM SPSS). Data were assessed for normality using the Shapiro-Wilk test. Parameters that were not normally distributed (i.e., Shapiro-Wilk P value>.05) were then log-transformed and rechecked for normality. Independent-sample, unpaired, 2-tailed t-tests (on either original variables or log transformed variables) were conducted to assess for differences between Groups A and B. The Levene test for the equality of variances was calculated, and if the significance was found to be less than .05, equal variances were not assumed. In many cases, the data did not give any indication that the populations were normal or even log-normal (predominantly because of outliers). For these variables, we used the non-parametric Mann-Whitney U test for comparing independent samples. For each task, data from the right eye were analyzed as no within group left-right eye differences were noted in the cohort. Given the challenges in normalizing all data, the number of subject measurement points varied from task to task.

Descriptive Data. There were 60 research subjects with symptomatic mTBI (Group A) and 26 control subjects without a history of TBI or symptoms (Group B). All Group A subjects were male and had a mean age of 23.2 years (SD=2.95). Two (3.0%) were African-American, 47 (78.3%) were Caucasian, 10 (16.6%) were Hispanic, and one (1.6%) was Native American. All 60 had experienced at least one mTBI, with the most recent TBI occurring a mean of 8.5 months (SD= 6.58 months, range= 3-39 months) prior to the baseline assessments. Cause of concussion included improvised explosive device (IED) blast (85.3%), rocket propelled grenades (3.0%), and mortar attacks (1.7%). The remaining 10% were uncategorized blasts. Slightly more than one-quarter of the participants self-reported additional concussions (M = 2.1, SD=.95, range=1-

4) prior to the most recent blast injury. The symptoms of the Group A cohort were characterized as mild on the RPQ symptomatic, with 7 of the 16 items endorsed in the range of 2 (a mild problem) and only one item (forgetfulness) in the range of 3 (a moderate problem).13 Importantly, the three vision-related items, blurred vision, light sensitivity and double vision, on the RPQ were reported as either never having been a problem or no longer a problem, so no subjects reported active difficulty with vision. Twenty six healthy undergraduate, graduate or post-graduate trainees served as controls. None had sustained a mild TBI and all were asymptomatic.

Saccades. Saccadic data from the horizontal and vertical target displacement tasks for subjects with symptomatic mTBI and controls were compared using 11 measures (see Table 1). Data from horizontal and vertical direction eye movements were analyzed for the horizontal and vertical target displacement tasks, respectively.

*** Insert Table 1 Here ***

Main Sequence Data for Saccadic Data. For each subject, peak velocity, peak acceleration, duration and saccadic amplitude data for all saccades were fit to the models for both horizontal and vertical displacement tasks. All fits were performed using the nonlinear curve fitting toolbox in MATLAB (Mathworks, MA). As is standard in the eye-tracking literature, exponential models were used for peak velocity and peak acceleration, while a power function model was used for duration.[28] This process generated the parameters asymptotic velocity, asymptotic acceleration, exponential rise (for both velocity and acceleration), predicted duration

of a 1 degree saccade, and the percentage rate of change for predicted duration of a 1-degree saccade, giving rise to 6 measures. The root-mean-square error for each of the three model fits was checked for goodness of fit. The RMSE was also compared between groups to see if one group had more variance than the other, adding 3 more measures. After curves were fit for each subject, the predicted peak velocity, peak acceleration, and duration from the models for 1 degree and 5 degree saccades were compared between symptomatic mTBI subjects and controls, providing 5 more measures. Figure 1 shows typical model fits for peak velocity, acceleration and duration.

*** Insert Figure 1 Here ***

Horizontal and Vertical Tracking Step Data. Of the 11 accuracy variables and the 14 main sequence variables, 11 (5 accuracy and 6 main sequence) variables show significant differences between Groups A and B for both horizontal and vertical displacement tasks (p-value < .05). Results are summarized in Tables 2 and 3.

*** Insert Tables 2 and 3 Here ***

Smooth Pursuit. Data for horizontal and vertical smooth pursuit tasks were analyzed using 7 measures (see Table 4). Data from eye movement in the horizontal and vertical directions were analyzed for the horizontal and vertical smooth pursuit tasks, respectively.

*** Insert Table 4 Here ***

Horizontal and Vertical Ramp Data. Of these seven variables, only two showed significant differences between Groups A and B (p-value < .05). No support was present in any of the cases for an assumption that data came from a normally distributed population even after log transformation. Accordingly, in our analysis, the non-parametric Mann-Whitney U test for comparing independent samples was used.

*** Insert Table 5 Here ***

Fixation. Fixation data for all subjects came from fixations between saccades from the horizontal target displacement task. To minimize the potential effect due to target eccentricity, only fixations around the origin were included in the analysis. Fixation was compared between groups using 10 measures (see Table 6).

*** Insert Table 6 Here ***

No differences were found using either parametric or non-parametric methods. Additionally, no results were found running parametric tests on log transformed data, which was closer to normally distributed.

Discussion

Diagnosing and monitoring recovery after mTBI, using either subjective or objective parameters, is challenging. Importantly, the study revealed significant differences in a number of eye

tracking components, both for tasks involving a step displacement of the target and for smooth pursuit tasks. Uncovering these differences represents a vital initial step towards development of objective tests which can discriminate between individuals with symptomatic mTBI and controls. This investigation represents the first examination of the utility of eye tracking to identify objective findings in individuals with subjective symptoms after mTBI using a non-mTBI control group for comparison. Given the challenges of both diagnosing and monitoring recovery after mTBI, using either subjective or objective parameters, this study represents a significant step forward.

Importantly, we found significant differences in two of the three eye tracking parameters studied: saccades and SPEM. Robust differences were found between responses of subjects with symptomatic mTBI and controls to horizontal and vertical stepwise target displacement tasks, with subjects with symptomatic mTBI having statistically larger position errors, smaller saccadic amplitudes, smaller predicted peak velocities, smaller peak accelerations, and longer durations. Subjects with symptomatic mTBI were also more likely to respond to step changes in target position with smaller primary saccades compared to controls. In general, symptomatic mTBI tracked the stepwise moving targets less accurately, revealing possible brain dysfunction. This investigation represents the first examination of the utility of eye tracking using a non-mTBI control group as a means to identify objective findings in individuals with subjective symptoms after mTBI. Differences in responses to smooth pursuit tasks were also found between subject groups, although not as robust as the differences between mTBI subjects and controls. Here, the saccadic amplitudes were significantly different. The amplitudes were larger for subjects with symptomatic mTBI for the horizontal smooth pursuit task. In comparison to controls, pursuit gain was lower among subjects with symptomatic mTBI. Surprisingly, in contrast to a number of

other neurological disorders, no differences were found between groups for fixation measures. Further investigation into the specificity and sensitivity of these measures in light of the often complex polytraumatic nature of individuals with either combat or civilian-related injury (e.g., presence of acute or chronic conditions, anxiety disorders, depression, pain and substance abuse) is warranted. This represents an important initial step in the understanding of the role of both eye movement abnormalities and computerized eye tracking in the diagnosis and monitoring of symptomatic mTBI. Specific linkages between symptoms, eye tracking abnormalities, and neuropathology (as revealed by neuroimaging) may be an important subsequent step.

The wide array of abnormalities uniquely found in the mTBI cohort may have contributed to their diverse complaints, including headache, blurred/double vision, dizziness, clumsiness, reading difficulties, and driving problems. Future studies correlating the magnitude and type of the range of eye movement errors with ecologic complaints would be a fruitful area of further investigation. These analyses could also assist in the development of both predictive models for symptom development and recovery, and in the development of effective treatments for specific symptom-eye tracking abnormality associations.

This study utilized standard protocols to define exposure to a PCE, to be symptomatic for PCS, and for eye tracking, which allowed us to remove much of the subjectively commonly encountered in mTBI research. However there were some limitations to the research design that may limit its generalizability. These include; gender, restricted age, etiology of mTBI, chronicity of mTBI and symptoms, variability in symptom treatments, and co-morbid conditions. These restrictions may be less significant, in particular to the Departments of Defense and Veterans Affairs systems, since the bulk of individuals with mTBI seen in these systems tend to be younger males with complex military theatre polytrauma injuries.[29] Future studies will focus on

larger samples of individuals that include cohorts with more discrete causes of symptom complex (e.g., isolated mTBI, isolated stress disorders, isolated pain complaints), in an attempt to identify unique patterns of eye movement abnormalities based on etiology of symptoms. Additionally, analyses of the impact of symptom patterns on eye movement seen, as well as the association between differential patterns of eye movement abnormalities with symptom presentations, can be performed with larger subject samples. Lastly, temporal associations between injury, symptom presentation, and eye movement abnormalities may be an important key to use of eye tracking to monitor recovery after mTBI.

References

1. http://newsfeed.time.com/2013/06/19/head-trauma-sensors-aim-to-measure-concussion-risks/; http://www.thedailybeast.com/newsweek/2010/11/08/

2. http://www.thedailybeast.com/newsweek/2010/11/08/veteran-s-head-injuries-confound-military-doctors.html

3. http://www.healthquality.va.gov/Rehabilitation_of_Concussion_mTBI.asp

4. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. *N Engl J Med* 2008; 358:453-463.

5. Brenner LA, Vanderploeg RD,Terrio H. Assessment and diagnosis of mild traumatic brain injury, posttraumatic stress disorder, and other polytrauma conditions: Burden of adversity hypothesis. *Rehabil Psych* 2009;54(3):239-246.

6. ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010, F07.2 Postconcussional syndrome, World Health Organization.

7. Arciniegas DB, Topkoff JL. Applications of the P50 evoked response to the evaluation of cognitive impairments after traumatic brain injury. *Phys Med Rehabil Clin N Am* 2004 Feb;15(1):177-203.

8. Gosselin N, Bottari C, Chen JK, Petrides M, Tinawi S, de Guise E, Ptito A. Electrophysiology and functional MRI in post-acute mild traumatic brain injury. *J Neurotrauma* 2011;28(3):329-41.

9. Nuwer MR, Hovda DA, Schrader LM, Vespa PM Routine and quantitative EEG in mild traumatic brain injury. *Clin Neurophysiol* 2005;116(9):2001-25.

10. Cohen BA, Inglese M, Rusinek H, Babb JS, Grossman RI, Gonena O. MR Spectroscopy and MRI-Volumetry in Mild Traumatic Brain Injury. *AJNR* 2007;28:907-913.

11. McAllister TW, Saykin AJ, Flashman LA, Sparling MB, Johnson SC, Guerin SJ, Mamourian AC, Weaver JB, Yanofsky N. Brain activation during working memory 1 month after mild traumatic brain injury: a functional MRI study. *Neurol* 1999;53(6):1300-8.

12. Yuh EL, Mukherjee P, Lingsma HF, Yue JK, Ferguson AR, Gordon WA, Valadka AB, Schnyer DM, Okonkwo DO, Maas AI, Manley GT; TRACK-TBI Investigators. Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. *Ann Neurol* 2013 Feb;73(2):224-35.

13. Buxton RB, Uludağ K, Dubowitz DJ, Liu TT. Modeling the hemodynamic response to brain activation. *Neuroimage* 2004;23 Suppl 1:S220-33.

14. Deppe M, Ringelstein EB, Knecht S. The investigation of functional brain lateralization by transcranial Doppler sonography. *Neuroimage* 2004;21(3):1124-46.

15. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation *Br J Anaesth* 2009;103 (suppl 1): i3-i13.

16. Pickett TC, Radfar-Baublitz LS, McDonald SD, Walker WC, Cifu DX. Objectively assessing balance deficits after TBI: Role of computerized posturography. *J Rehabil Res Dev* 2007;44(7):983-90.

17. Guskiewicz KM, Ross SE, Marshall SW. Postural Stability and Neuropsychological Deficits After Concussion in Collegiate Athletes. J Athl Train 2001;36(3):263-273.

18. Brenner LA, Terrio H, Homaifar BY, Gutierrez PM, Staves PJ, Harwood JE, Reeves D, Adler LE, Ivins BJ, Helmick K, Warden DF. Neuropsychological test performance in soldiers with blast-related mild TBI. *Neuropsychol* 2010;24(2):160-7.

19. Ceranic B, Prasher D, Raglan E, Luxon L. Tinnitus after head injury: evidence from otoacoustic emissions *J Neurol Neurosurg Psychiatry* 1998; 65(4): 523–529

20. http://www.dcoe.health.mil/Content/navigation/documents/Portable%20Field-Based%20Devices%20for%20the%20Early%20Diagnosis%20of%20mTBI.pdf

21. Kraus MF, Little DM, Donnell AJ, Reilly JL, Simonian N, Sweeney JA. Oculomotor Function in Chronic Traumatic Brain Injury. *Cog Behav Neurol*. 2007; 20(3): 170-178. PMID:17846516

22. Heitger MH, Jones RD, Anderson TJ. A new approach to predicting postconcussion syndrome after mild traumatic brain injury based upon eye movement function. *Conf Proc IEEE Eng Med Biol Soc*. 2008; 2008:3570-3. doi: 10.1109/IEMBS.2008.4649977

23. Ciuffreda, LLudlam D, Thiagarajan P. Oculomotor diagnostic protocol for the mTBI population. *Optometry*. 2011; 82(2): 61-63. doi: 10.1016/j.optm.2010.11.011.

24. Ramat S, Leigh RJ, Optican LM. What clinical disorders tell us about the neural control of saccadic eye movements. *Brain*. 2007; 130: 10-35. doi: 10.1093/brain/awl309.

25. Suh M, Kolster R, Sarkar R, McCandliss B, Ghajar J, Cognitive and Neurobiological Research Consortium. Deficits in predictive smooth pursuit after mild traumatic brain injury. *Neurosci Lett.* 2006; 401(1-2): 108-113. doi: 10.1016/j.neulet.2006.02.074.

26. Cifu DX, Hart BB, West SL, Walker WC, et al. The effect of hyperbaric oxygen on persistent post-concussive symptoms. J Head Trauma Rehabil. doi: 10.1097/HTR.0b013e3182a6aaf0

27. Eyres S, Carey, A, Gilworth, G., Neumann V, Tennant, A. Construct validity and reliability of the Rivermead post-concussion symptoms questionnaire. Clinical Rehabil 2005 19(8), 878-887

28. Leigh, R. John, Zee, David S. The Neurology of Eye Movements, Oxford University Press:2006.

29. Cifu DX, Blake P: Overcoming Post-Deployment Syndrome: A Six-Step Mission to Health. DemosHealth, New York, 2011.

Table 1
Measures for Comparing Saccadic Data

Number of Primary Saccades: the number of times the subject made at least one saccadic movement following a target movement (if target moved again before the subject then no primary saccade was recorded)
Number of correcting saccades: the total number of saccades excluding the primary saccades following the target movements
Average Latency: the mean reaction time to each target movement
Primary Position Error: the absolute value of the difference between the target displacement and the amplitude of the primary saccades. Three sub-measures of primary position error were calculated: • **Mean of the Normalized Position Error.** the mean of the absolute value of the ratio between the position error and the target amplitude. Normalization attempts to account for the dependency of the amplitude of the position error on the amplitude of the target displacement. • **Standard Deviation of the Ratios of the Position Error and the Target Displacement.** • **Mean of the Absolute Value of the Non-normalized Position Errors.**
Final Position Error: the absolute value of the difference between the target displacement and the position of the eye before the next target movement. The same three sub-measures for primary position error were calculated for final position error.
Mean of the Absolute Value of the Normalized Primary Saccadic Amplitude: the mean of the absolute value of the ratio between the primary saccadic amplitude and the target amplitude for all saccades per individual. Here, normalization attempts to account for the dependency of the amplitude of the primary saccades on the amplitude of the target displacement.
Mean Q-Ratio: the mean of the ratio between peak velocity and saccadic amplitude over all saccades per individual.

Table 2
Horizontal Displacement Task

HORIZONTAL TRACKING	**Mean Group A**	**Mean Group B (control)**	**Significance Level**	**Type of test***
Mean of normalized primary position error	.4255	.2043	.000	nonparametric
SD of normalized primary position error	.6993	.3502	.000	nonparametric
Mean of normalized final position error	.2993	.1346	.016	nonparametric
Mean of non-normalized primary position error	4.7572	2.3803	.000	nonparametric
Number of primary saccades	20.64	24.92	.000	nonparametric
Predicted Velocity, 1-deg amp	55.4612	59.4678	.008	parametric
Predicted Velocity, 5-deg amp	219.71	235.51	.001	parametric
Predicted Acceleration, 1-deg amp	3464.97	3712.18	.026	parametric
Predicted Acceleration, 5-deg amp	12495.4	13530.74	.003	parametric
Predicted Duration, 1-deg amp	36.60	34.71	.000	nonparametric
Predicted Duration, 5-deg amp	61.62	56.93	.000	nonparametric

CAPTION: 55 Group A and 26 Group B had complete results for all of the horizontal target displacement tasks

*In all cases in this table, the employment of nonparametric rather than parametric tests did not affect whether the difference between groups was significant.

Table 3
Vertical Displacement Task

VERTICAL TRACKING	**Mean Group A**	**Mean Group B (control)**	**Significance Level**	**Type of test***
Mean of normalized primary position error	.4093	.2523	.002	parametric
SD of normalized primary position error	.5737	.3416	.011	nonparametric
Mean of normalized final position error	.3184	.1817	.004	parametric
Mean of non-normalized primary position error	3.0513	1.9616	.054*	parametric
Number of primary saccades	22.74	24.72	.000	nonparametric
Predicted Velocity, 1-deg amp	52.61	58.94	.000	parametric
Predicted Velocity, 5-deg amp	213.5	229.9	.001	parametric
Predicted Acceleration, 1-deg amp	3121.93	3508.92	.000	parametric
Predicted Acceleration, 5-deg amp	11714.6	12906.8	.000	nonparametric
Predicted Duration, 1-deg amp	39.36	35.97	.000	parametric
Predicted Duration, 5-deg amp	66.67	59.78	.000	nonparametric

CAPTION: 47 Group A and 26 Group B had complete results for all of the vertical target displacement tasks.

*In all cases in this table, the employment of nonparametric rather than parametric tests did not affect whether the difference between groups was significant.

Table 4
Measures for Comparing Smooth Pursuit Data

Number of Saccades: the total number of saccades during a smooth pursuit task
Mean Gain: the mean of the ratios of eye velocity and target velocity between saccades
Minimum Gain: the minimum of the ratios of eye velocity and target velocity between saccades
Maximum Gain: the maximum of the ratios of eye velocity and target velocity between saccades
Mean Absolute Saccadic Amplitude: the mean of the absolute value of saccadic amplitude calculated across all saccades during the tasks
Mean Duration: the mean length of time eyes are smoothly pursuing the target between saccades
Mean Absolute Normalized Saccadic Amplitude: the mean of the absolute value of the ratio of saccadic amplitude and target velocity. Normalization by target velocity attempts to account for dependency of saccadic amplitude on the velocity of the target.

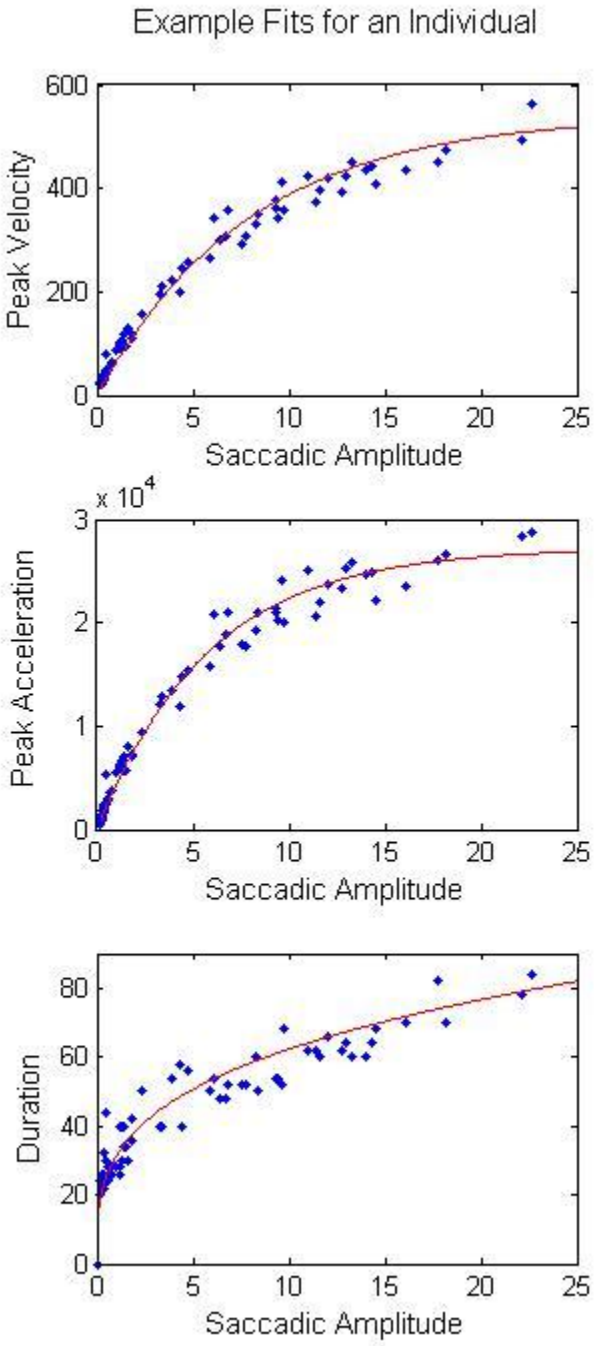
Table 5
Smooth Pursuit Ramp Data

HORIZONTAL RAMP	Mean Group A	Mean Group B (control)	Significance Level
Min Gain	.0804	.1088	.000
Mean normalized amplitude	.2208	.1561	.017

VERTICAL RAMP	Mean Group A	Mean Group B (control)	Significance Level
Min Gain	.0761	.1013	.011
Mean normalized amplitude	.2253	.2933	.016

CAPTION: 55 Group A and 24 Group B had complete results for all of the horizontal smooth pursuit tasks; 49 Group A and 23 Group B had complete results for all of the vertical smooth pursuit tasks

Figure 1
Sample Model Fits



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Caption: Example model fits for an individual subject. Peak Velocity, Acceleration and Duration versus Saccadic Amplitude (Top, Middle and Bottom, respectively). The blue dots represent absolute values of data recorded from a horizontal step displacement task. The red lines are the corresponding model fits.