

Eye Tracking Detects Disconjugate Eye Movements Associated with Structural Traumatic Brain Injury and Concussion

Uzma Samadani,^{1–3} Robert Ritlop M. Eng,³ Marleen Reyes,^{2,3} Elena Nehrbass,^{2,3} Meng Li,¹ Elizabeth Lamm,³ Julia Schneider,³ David Shimunov,³ Maria Sava,³ Radek Kolecki,³ Paige Burris,³ Lindsey Altomare,³ Talha Mehmood,³ Theodore Smith,⁴ Jason H. Huang,⁵ Christopher McStay,⁶ S. Rob Todd,⁷ Meng Qian,¹ Douglas Kondziolka,³ Stephen Wall,⁶ and Paul Huang³

Abstract

Disconjugate eye movements have been associated with traumatic brain injury since ancient times. Ocular motility dysfunction may be present in up to 90% of patients with concussion or blast injury. We developed an algorithm for eye tracking in which the Cartesian coordinates of the right and left pupils are tracked over 200 sec and compared to each other as a subject watches a short film clip moving inside an aperture on a computer screen. We prospectively eye tracked 64 normal healthy noninjured control subjects and compared findings to 75 trauma subjects with either a positive head computed tomography (CT) scan ($n = 13$), negative head CT ($n = 39$), or nonhead injury ($n = 23$) to determine whether eye tracking would reveal the disconjugate gaze associated with both structural brain injury and concussion. Tracking metrics were then correlated to the clinical concussion measure Sport Concussion Assessment Tool 3 (SCAT3) in trauma patients. Five out of five measures of horizontal disconjugacy were increased in positive and negative head CT patients relative to noninjured control subjects. Only one of five vertical disconjugacy measures was significantly increased in brain-injured patients relative to controls. Linear regression analysis of all 75 trauma patients demonstrated that three metrics for horizontal disconjugacy negatively correlated with SCAT3 symptom severity score and positively correlated with total Standardized Assessment of Concussion score. Abnormal eye-tracking metrics improved over time toward baseline in brain-injured subjects observed in follow-up. Eye tracking may help quantify the severity of ocular motility disruption associated with concussion and structural brain injury.

Key words: concussion; cranial nerve palsy; disconjugate; eye movement tracking; ocular motility

Introduction

GROSS ASSESSMENT OF EYE MOVEMENT CONJUGACY IS commonly performed by health care providers to assess global neurological and ophthalmic functioning. In stable patients, more detailed examinations to assess the alignment of the eyes include the cover test and Hirschberg corneal reflex test. Other tests used to assess binocular conjugacy include the Titmus House Fly test,

Lang's stereo test, the Hess screen, red-filter test, Maddox rod evaluation, and Lancaster red-green test. In young children, who may be less cooperative with an examiner, binocular gaze conjugacy may only be assessable with simpler algorithms, such as following an object moving in a set trajectory.¹ The ability to focus both eyes on a single point in space requires intact vergence; experienced optometrists detect vergence disorders in up to 90% of patients with "mild" brain injury resulting from blast² or concussion.^{3–6}

¹Steven and Alexandra Cohen Veterans Center for Post-Traumatic Stress and Traumatic Brain Injury at NYU Langone Medical Center, ³Department of Neurosurgery, ⁴Department of Ophthalmology, ⁶Department of Emergency Medicine, ⁷Department of Trauma Surgery, New York University School of Medicine, New York, New York.

²Department of Neurosurgery, New York Harbor Health Care System, New York, New York.

³Department of Neurosurgery, Baylor Scott & White Neuroscience Institute, Temple, Texas.

We have developed a novel eye-movement-tracking algorithm that appears useful for quantitating the coordination of eye movements during naturalistic viewing.⁷ It is performed while a subject watches television or a video playing inside a moving aperture with a set trajectory for 200 sec at a fixed distance from a viewing monitor. The position of each pupil is recorded over time elapsed as the video travels on its time course, enabling detection of impaired ability to move the pupils relative to time and therefore relative to each other.

Recently, we described how a monocular version of this technique detects cranial nerve III and VI palsies, which can be associated with acute supra- and infratentorial mass effect and elevated intracranial pressure.⁸ Our data suggested that mass effect within the brain may result in decreased vertical eye movement if supratentorial and decreased horizontal eye movement if infratentorial. Binocular tracking provides richer information than monocular tracking because the position of the pupils can be compared to each other in real time, enabling detection of subtle differences, as have been observed to occur with concussion.³⁻⁶

We hypothesized that this binocular eye-tracking algorithm would detect disconjugacy in traumatic brain-injured patients, relative to control subjects, regardless of whether the trauma was apparent on brain imaging with CT (computed tomography) scan. To test this hypothesis, we eye tracked 75 trauma patients and 69 noninjured control subjects as they watched music videos played on the viewing monitor of a portable binocular tracking device. The videos played continuously inside an aperture one eighth the screen size that moved clockwise around the perimeter of the monitor at a rate of 10 sec per side.

Methods

Patient selection

Control subjects were employees, volunteers, visitors, and patients at the Bellevue Hospital Center (New York, NY) recruited in accord with institutional review board policy. Inclusion criteria were age 7–76 years, vision correctable to within 20/50 bilaterally, intact ocular motility, and ability to provide a complete ophthalmologic, medical, and neurological history as well as medications/drugs/alcohol consumed within the 24h before tracking. Exclusion criteria were history of: strabismus, diplopia, palsy of cranial nerves III, IV, or VI, papilledema, optic neuropathy, macular edema, retinal degeneration, dementia or cognitive impairment, hydrocephalus, sarcoidosis, myasthenia gravis, multiple sclerosis, or other demyelinating disease. Pregnant individuals and prisoners were excluded from the study as were subjects who were missing eyes, not opening eyes, or wearing excessive mascara/false eyelashes. Subjects reporting any minor brain injury regardless of loss of consciousness (LOC) within the previous week were also excluded from participating as controls.

All trauma patients were recruited from the Bellevue Hospital emergency services (emergency room [ER] and trauma bay), trauma service, and neurosurgery service. They were between the ages of 18 and 60, subject to the same exclusion requirements as controls, consentable and able/willing to participate in the study. Some patients were observed in the ER for up to 3 days, whereas others were recruited from the inpatient services.

Both positive and negative head CT patients needed to have obtained a CT scan of the head before consideration for study enrollment. Trauma exclusion criteria included patients suffering burns, anoxic injury, or multiple/extensive injuries resulting in any medical, surgical, or hemodynamic instability. Positive head CT was defined as final CT scan reading (by an attending physician radiologist) demonstrating the presence of hemorrhage (subdural, epidural, subarachnoid, or intraparenchymal), brain contusion, or

full-thickness skull fracture consistent with acute brain injury. Positive head CT patients were considered eligible for recruitment for up to 2 weeks after injury or surgery as long as they exhibited evidence of not yet being fully recovered from the brain injury (e.g., were still hospitalized). No positive head CT patients were recruited preoperatively; they either had nonsurgical injuries or were recruited postsurgically.

Criteria for obtaining a head CT in the ER and trauma bay were based on an amalgamation of Canadian⁹ and New Orleans Criteria,¹⁰ in accord with the judgment of the individual examining physician responsible for the care of the patient. All aspects of patient care, including interpretation of radiology films, were rendered by personnel blinded to the results of eye-tracking research. Research subjects were not told about the findings of their eye-tracking studies. Research personnel conducting the Sport Concussion Assessment Tool 3 (SCAT3) assessments were able to view eye-tracking trajectories to ensure that the study was done, but did not view individual metrics associated with the study.

Negative head CT patients were defined as having no signs of structural injury on imaging; however, complaining of brain injury symptoms, such as headache, dizziness, cognitive impairment, and so on, as manifested by at least one of the following: LOC for any amount of time <30 min; any loss of memory for events immediately before or after the accident; any alteration in mental state at the time of accident (i.e., feeling dazed, disoriented, or confused); and focal neurological deficit(s) that may or may not be transient.

Non-head-injured was defined as patients who had sustained trauma, but did not meet ER/trauma bay criteria for obtaining a CT scan of the brain. Additional exclusion criteria for this group were: complaining of brain injury symptoms, such as headache, dizziness, cognitive impairment, and so on, as manifested by at least one of the following: any period of LOC; any loss of memory for events immediately before or after the accident; any alteration in mental state at the time of accident (i.e., feeling dazed, disoriented, or confused); and focal neurological deficit(s) that may or may not be transient.

Visual stimulus

We recorded subjects' eye movements with an Eyelink 1000 eye tracker at a fixed distance of 55 cm from a computer monitor over a time period of 220 sec. Subjects were seated in either a height-adjustable or height-fixed chair or bed, with the monitor height adjusted to the subject. The tracker chinrest was attached to the monitor. The visual stimuli were the music videos Shakira Waka-Waka, K'naan Wavin' Flag, the Under the Sea song from the Little Mermaid, "I Just Can't Wait to be King" from the Lion King, Puss in Boots (soundtrack), Michael Jackson's "Man in the Mirror," or Shankar Ehsan Loy "Bhumbroo." The video was played continuously in a square aperture with an area approximately one eighth the screen size while moving clockwise along the outer edges of the monitor for five complete cycles of 40 sec each. The first and last 10 sec of each data set were discarded to yield 200 sec of data. The afferent stimulus was presented binocularly, and eye tracking was performed binocularly. Subjects were not spatially calibrated to the tracker to enable independent analysis of each pupil position over time.

Data analysis

The eye tracker sampled pupil position at 500 Hz, yielding 100,000 samples over 200 sec. We created scatter plots of the entire time series by plotting the 100,000 (x,y) pairs representing the two orthogonal components of the instantaneous angle of pupil reflection over time to create "box trajectories" that reflected the temporal nature of the pupillary movement. Two hundred data points before and after each blink were removed before creating the measures of disconjugacy and aspect ratio to limit noise in the data from the blink event.

Analysis of gaze disconjugacy

Comparing the movement of one eye of a subject to the other eye of a subject was performed by comparing the x,y Cartesian coordinates at any time point t, for example, by subtracting the x coordinate of the left eye from the x coordinate of the right eye or vice versa; also, by subtracting the y coordinate of the left eye from the y coordinate of the right eye or vice versa. The sums of the differences between all of the x coordinates over the time tested informs regarding horizontal movement of the pupil. The sums of the differences in y coordinates over time informs regarding vertical movement of the pupil. The total sum of the differences between both x and y coordinates over the time tested can be summed to obtain a measure of total disconjugacy of gaze, or as an average of five eyebox trajectory cycles formulaically represented as follows:

$$X_{Avg,ik} = \frac{\sum_{j=1}^5 X_{ijk}}{5}, \text{ for all } i = 1:N, k = 1:2,$$

where X_{ijk} refers to the x coordinate of the pupil, and k refers to the left or right eye of a subject. In cases where a subject's data were missing at any given time point in the five cycles (including blinks), the denominator of the equation was the number of cycles where the data were present. The difference in the x and y position, for the left and right eye, may then be computed. This vector of difference may then be plotted graphically for purposes of assessment and interpretation. To have a single metric expressing the level of pupil disconjugation, a variance of the data may be computed with respect to an expected mean of zero. This is significant because the code assumes that a healthy subject has zero vertical or horizontal pupil position difference between each eye. The variance for either horizontal (x) or vertical (substitute y for x) movement may be computed as follows:

$$Var_x = \frac{1}{N} \sum_{i=1}^N ((X_{Avg,i1} - X_{Avg,i2}) - 0)^2$$

The total variance in both the horizontal and vertical planes may be computed as follows:

$$Var_{Tot} = Var_x + Var_y.$$

The variance in x, y, and the total variance may be plotted in order to assess the amount of disconjugacy present in a subject.

Statistical analyses

Data analysis was performed using R (version 3.0.3; R Foundation for Statistical Computing, Vienna, Austria) and SAS statistical software (version 9.3; SAS Institute Inc., Cary, NC). A *p* value of <0.05 after being adjusted for multiple comparisons was deemed statistically significant.

Kruskal-Wallis' test was used to compare age, eye-tracking parameters, symptom severity score, and Standardized Assessment of Concussion (SAC) score across groups. A significant result indicated a difference between at least two of the groups. *p* values adjusted for multiple comparisons were obtained using the bootstrap method,^{11,12} a resampling-based multiple testing method for correlated variables. Multiple pair-wise comparisons for eye-tracking parameters, symptom severity score, and SAC were made using Wilcoxon's two-sample tests. *p* values were first adjusted by bootstrap method for correlated variables and then adjusted by Bonferroni's method for multiple testing within a single variable.

Linear regression was performed to find the relationship between tracking metrics and SAC as well as the relationship between

tracking metrics and the symptom checklist of SCAT3. *p* values were adjusted using the bootstrap method.

Results

We recruited 64 noninjured control subjects, 23 trauma patients who were deemed by the ER or trauma staff to have no indication for head CT (the nonhead injury group), 39 patients who underwent head CT that was read as negative for acute trauma by the attending radiologist (negative CT), and 13 structurally brain injured (positive head CT) patients.

There was no statistically significant difference in age, gender, or handedness among trauma groups or relative to normal controls. The means for age with all groups was between 35 and 40 years of age (Table 1; Kruskal-Wallis' test, *p*=0.428; chi-square, 2.77). The control group was 47.9% female, the nonhead injury group was 39.0% female, the negative head CT group was 44.4% female, and the positive head CT group was 35.9% female. The positive head CT group versus controls trended toward more males with a *p* value of 0.071. One non-head-injured patient, 2 in the negative CT group, and 1 positive CT patient were left handed. There were also no significant differences in elapsed time between presentation to the hospital and eye tracking among the trauma groups. The mean times were 22.5 ± 44.8 h for the non-head-injured group, 30.9 ± 80.4 h for the negative head CT group, and 24.6 ± 19.7 h for the positive head CT group. Causes of trauma are summarized in Table 2.

Medications consumed by patients in each group within the 24 h before eye tracking were also documented. In the CT-negative group, the most common medications were Tylenol (*n*=4), Percocet (*n*=5), morphine (*n*=5), Colace (*n*=4), ibuprofen (*n*=5), and senna (*n*=5). In the CT-positive group, the most common medications were keppra (*n*=11), morphine (*n*=5), Tylenol (*n*=4), and heparin (*n*=4). In the non-head-injured group, the only medication consumed by more than 3 patients was Percocet (*n*=5).

Disconjugacy of eye movements were evaluated in sum, in the x and y planes for the total box trajectory, and in the x and y planes individually for each segment of the aperture trajectory as it moved around the perimeter of the viewing monitor. Comparison was made to a normal control group. Significant differences in horizontal disconjugacy were noted in all four segments of the box trajectory (summary, Table 3; Figs. 1 and 2; Kruskal-Wallis' test, *p*<0.002 for horizontal disconjugacy in each side of trajectory) in positive and negative head CT patients relative to control subjects. Only one segment of vertical disconjugacy, as the eye traveled along the bottom trajectory of the rectangular stimulus, was significantly disconjugate in brain-injured subjects relative to controls (Table 3).

The symptom severity score of the SCAT3 was greater in positive and negative head CT patients than in non-brain-injured

TABLE 1. SUMMARY STATISTICS FOR AGE

Variable	Observations	Minimum	Maximum	Mean	SD
Age Control	64	7.9620	75.488	36.498	15.454
Age non-head-injured	23	20.504	53.336	35.083	9.632
Age CT ⁻	39	21.810	59.135	39.637	10.847
Age CT ⁺	13	21.812	59.644	38.505	14.248

CT, computed tomography; SD, standard deviation.

TABLE 2. CAUSES OF TRAUMA

Causes of trauma	Non-head-injured	Negative head CT	Positive head CT
Domestic activity	0	4	0
Construction/industrial	6	4	1
Pedestrian vs. vehicle	5	11	2
Bicycle	3	6	3
Motor vehicle	4	5	2
Falls	1	4	3
Sports	3	1	1
Assaults	1	4	1
Total	23	39	13

CT, computed tomography.

controls (Table 4; Kruskal-Wallis' test, $p=0.002$; chi-squared, 13.036). There was no difference in symptom severity between CT⁻ and CT⁺ patients ($p=1.00$; adjusted Bonferroni).

The SAC was significantly decreased in positive CT patients (Table 5; Kruskal Wallis' test, $p=0.013$; chi-squared, 8.765) and

TABLE 3. P VALUES RESULTING FROM COMPARISON OF EYE TRACKING METRICS FOR TRAUMA SUBJECTS RELATIVE TO NONINJURED CONTROLS

Metric	Comparison	p value
Horizontal conjugacy	non-head-injured vs. control	0.819
	CT ⁻ vs. control	0.003
	CT ⁺ vs. control	0.048
Top	non-head-injured vs. control	0.144
	CT ⁻ vs. control	0.042
	CT ⁺ vs. control	0.030
Right	non-head-injured vs. control	1.000
	CT ⁻ vs. control	0.003
	CT ⁺ vs. control	0.048
Bottom	non-head-injured vs. control	1.000
	CT ⁻ vs. control	0.015
	CT ⁺ vs. control	0.045
Left	non-head-injured vs. control	0.417
	CT ⁻ vs. control	0.021
	CT ⁺ vs. control	0.096
Vertical conjugacy	non-head-injured vs. control	1.000
	CT ⁻ vs. control	0.342
	CT ⁺ vs. control	1.000
Top	non-head-injured vs. control	1.000
	CT ⁻ vs. control	0.057
	CT ⁺ vs. control	1.000
Right	non-head-injured vs. control	1.000
	CT ⁻ vs. control	1.000
	CT ⁺ vs. control	1.000
Bottom	non-head-injured vs. control	1.000
	CT ⁻ vs. control	0.045
	CT ⁺ vs. control	0.048
Left	non-head-injured vs. control	1.000
	CT ⁻ vs. control	0.498
	CT ⁺ vs. control	0.243
Total conjugacy	non-head-injured vs. control	1.000
	CT ⁻ vs. control	0.069
	CT ⁺ vs. control	0.300

CT, computed tomography.

trended toward significance in negative head CT subjects relative to non-head-injured trauma subjects (Table 5).

Balance testing (Balance Error Scoring System) was not significantly different in the two brain-injured groups relative to non-head-injury trauma. Balance testing was only performed in 26 of 75 total trauma subjects given that the majority of trauma patients had either other injuries that precluded participation in balance testing or declined to participate in testing.

Linear regression analysis of all 75 trauma patients demonstrated that three metrics for horizontal disconjugacy positively correlated with SCAT3 symptom severity score and negatively correlated with total SAC score (Table 6).

Although all patients were asked to come in for serial follow-up examination, only 39 of 75 trauma patients returned at least once. Overall, 11 of 23 non-head-injured patients, 22 of 39 negative head CT patients, and 6 of 13 positive head CT patients returned. Though there were no differences in symptom severity among those who returned for follow-up versus those who did not in the CT⁻ or CT⁺ groups, among the non-head-injured controls, those with more symptoms on SAC assessment were more likely to return for follow-up (Mann-Whitney's test, $p=0.005$).

Trauma patients who presented for serial follow-up examination were compared to control subjects who underwent retesting. Additionally, comparison of metrics disrupted in 9 structurally and 22 nonstructurally brain-injured subjects followed over time demonstrated recovery toward normal control values (Figs. 3 and 4). Positive head CT subjects remained significantly different from serially tracked normal controls in four of five measures of horizontal disconjugacy at >4 weeks from injury, whereas negative head CT subjects were not significantly different from serially tracked uninjured controls at >4 weeks from injury.

Finally, we performed receiver operating characteristic (ROC) curve analysis for each of the horizontal conjugacy eye-tracking metrics relative to whether a CT scan was read as positive by the attending radiologist. The analyses use the CT⁺ or control as outcome and use the horizontal metrics as a predictor (Table 7). The cutoff points were chosen by the maximum of the Youden Index (sensitivity + specificity = 1), and analysis is limited by sample imbalance ($N[CT^+] = 13$; $N[control] = 64$). Kruskal-Wallis' yields were of $p < 0.05$ for the distribution of the areas under the curve (AUCs) over the patient groups.

Discussion

Eye tracking detects deficits in conjugacy of eye movements associated with positive and negative head CT brain injury. These tracking metrics correlate with extent of symptoms assessed with SCAT3, and improve over time, suggesting that eye tracking may quantitate physiological impact of brain injury regardless of whether it is apparent on CT scan, as is commonly noted in concussion.

We propose that eye tracking may be useful as a measure for the physiological impact of brain injury on ocular motility, rather than as a screening test for positive CT. One might consider that 2 patients with virtually identical CT scans in terms of the amount of blood present after trauma might have completely different physiological impact from those injuries. A patient with more cerebral atrophy may be asymptomatic, whereas a patient with none may be more neurologically distressed and impacted. Though both patients may have a "positive CT" with two pixels of blood, one may be much sicker than the other and have considerably worse eye-tracking metrics.

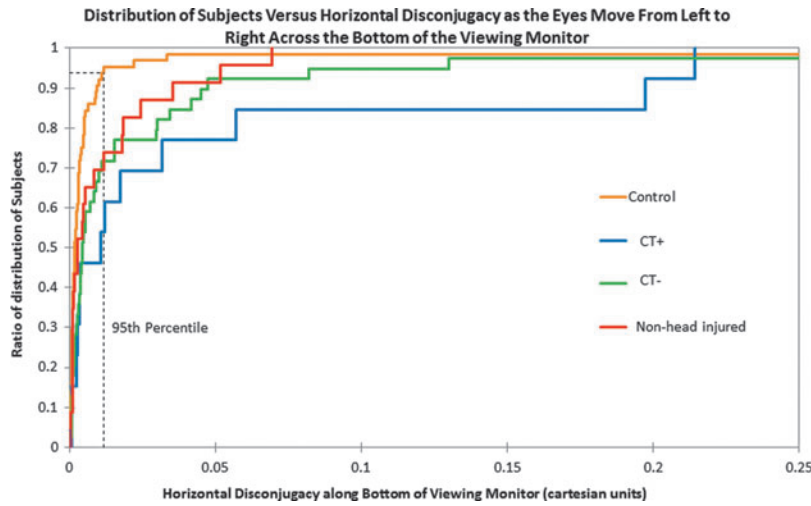


FIG. 1. Relative distribution of trauma patients and noninjured controls (y-axis) versus disconjucy (x-axis) to demonstrate that control subjects have the greatest proportion of patients with low horizontal disconjucy and positive CT patients have the highest proportion of patients with high horizontal disconjucy as the eyes move along the bottom segment of the box trajectory. Negative CT patients have a disconjucy in between positive CT and non-head-injured control subjects. Kruskal-Wallis’ statistical analysis yielded a value of $p < 0.05$ for CT⁺ and CT⁻ relative to noninjured controls. CT, computed tomography. Color image available online at www.liebertpub.com/neu

The ocular examination has remained a key component of the physical examination of traumatic brain-injured patients for at least 3,500 years, as documented by the ancient Egyptian Edwin Smith papyrus case detailing disconjucate gaze associated with a comminuted skull fracture.¹³ More than 65% of military brain injuries result in symptomatic vision difficulties.² Many of these ophthalmologic abnormalities, however, are subtle and require a trained examiner and stable, cooperative subject, if they can be detected at all. Vergence disorders,³⁻⁶ in which the eyes do not simultaneously adjust to view a single point, can be one such ophthalmologic disorder.

Eye movement tracking for neuropsychiatric and brain injury research^{14,15} has been performed for nearly 30 years and can evaluate smooth pursuit, saccades, fixation, pupil size, and other aspects of gaze. Spatial calibration of the eye tracker is generally performed for each individual being tracked. With calibration, the

eye tracker measures the relative position of pupil and corneal reflection for a period of about 400–800 ms while the subject looks at a target or targets of known position to generate meaningful spatial coordinates during subsequent pupil movement. The process of spatial calibration implies relatively preserved neurological function because it requires that the subject is able to follow commands and look at specific points.

Others have used eye tracking for assessment of concussion patients, but have focused on attention and gaze fixation after spatial calibration^{16,17} rather than assessing the capacity for normal eye movement. This capacity is not possible to assess with spatial calibration because the process of calibration may mask deficits in ocular motility. If there is a persistent and replicable weakness in movement of an eye, the camera will interpret the eye’s ability to move in the direction of that weakness as the full potential

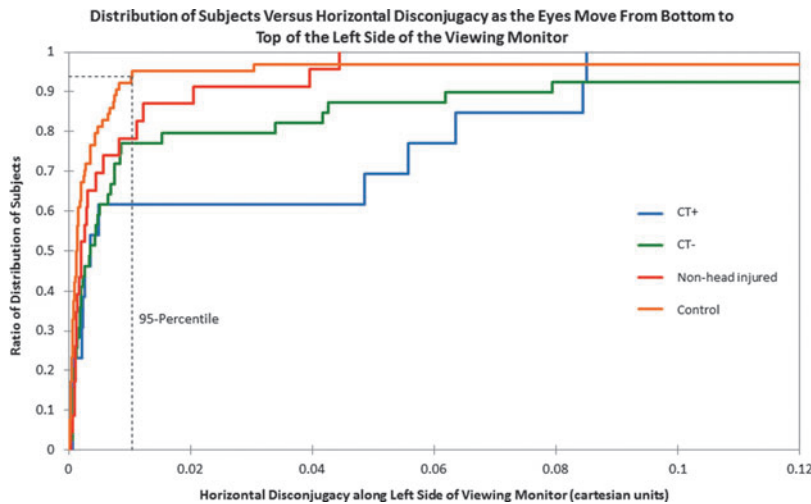


FIG. 2. Left segment of the box trajectory was disconjucate in the horizontal plane in positive and negative CT brain-injured subjects, but not in non-head-injured subjects relative to noninjured controls. Kruskal-Wallis’ statistical analysis yielded a value of $p < 0.05$ for CT⁺ and CT⁻ relative to noninjured controls. CT, computed tomography. Color image available online at www.liebertpub.com/neu

TABLE 4. SUMMARY STATISTICS FOR SYMPTOM SEVERITY SCORE SUBSET OF THE SCAT3 (COMPARISON TO NON-HEAD-INJURED)

<i>Symptom severity score</i>	<i>Observations</i>	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>SD</i>	<i>p values</i>
Non-head-injured	23	1.000	74.000	19.304	17.543	1.000
CT ⁻	39	1.000	104.000	40.744	28.676	0.006
CT ⁺	13	8.000	82.000	46.231	25.505	0.006

SCAT3, Sport Concussion Assessment Tool 3; CT, computed tomography; SD, standard deviation.

range of motion in that direction owing to the calibration process. In other words, if the subject is directed to look at a position, but consistently only moves halfway there, the calibration process will account for that when tracking subsequent eye movements and interpret movements to the halfway point as occurring at the full range of normal motion. If, during calibration, one eye only makes it halfway to the target, but the other eye is fully there, the camera will interpret both eyes as being together when one performs half the eye movement as the other. Thus, binocular spatial calibration may preclude detection of disconjugate gaze unless each eye is calibrated separately using a dichoptic apparatus.¹⁸

With spatial calibration, eye tracking essentially measures how well someone follows instructions with their eye movements.^{16,17} The algorithm we have developed does not actually care what the patient is looking at—it is measuring how well the eyes are capable of moving together (how coordinated they are) relatively independently of where the subject is looking (attention and gaze fixation).

We have developed a novel technique for nonspatially calibrated tracking performed while subjects watch a music video moving inside an aperture on a computer monitor. The aperture moves around the monitor periphery at a known rate so that the positions of the pupil can be compared at any given time by subtracting their Cartesian coordinates. By using temporal, rather than spatial, calibration, our method detects impaired ability to move one pupil relative to the other. Nonspatially calibrated tracking not only does not compensate for impaired motility, but also can be used in patients who do not follow commands, such as aphasics, foreign-language speakers, persistently vegetative individuals, and small children. It can also be used on animals.

Our algorithm detects deficits in conjugacy of eye movements associated with positive and negative CT brain injury that correlate with extent of symptoms assessed using a standardized outcome measure, suggesting that eye tracking may be useful for quantitation of the extent of injury associated with concussion. Eye movements in the horizontal, but not vertical, plane were significantly disconjugate in positive and negative head CT brain-injured patients relative to control subjects.

Some individual patients in the non-head-injured control trauma group also had tracking metrics in the range of brain-injured patients. This may reflect that particular eye movement metrics are

reflecting qualities of trauma (e.g., pain or sympathetic response) not exclusive to the brain.

Y-disconjugacy did not show significant differences between controls and brain trauma subjects, except at the bottom of the box trajectory (Table 3), which, on regression, did not correlate with severity of concussion symptoms. Y-disconjugacy may thus be a less-specific or -sensitive indicator of brain injury than x-disconjugacy.

The advantages of our algorithm over other methods for quantitating the extent of nonstructural brain injury are its quantitative objectivity and potential utility in subjects who have not had baseline testing. The most replicably reliable component of the baseline-requiring cognition assessment IMPACT test marketed to assess concussion is its visuomotor section.¹⁹ Currently, there is thought to be a significant need for objective measures of concussion in order to develop therapeutics and prophylactics for this most common form of brain injury.

Our algorithm should not be considered a proxy for assessment of full range of ocular motion. If the subject's eyes are positioned 55 cm from the center of the 30×35 cm viewing monitor, the algorithm elicits pupil movement in a maximum range of approximately 15 degrees in any direction from mid-position or approximately 30 degrees total from top to bottom or side to side. Thus, the algorithm does not require or assess the full range of ocular motility nor the entire visual field. These aspects could, in principle, be assessed through the use of a larger monitor or one positioned closer to the subject.

Our data demonstrated no significant difference in balance testing between bodily trauma subjects and brain-injured trauma subjects. In contrast, one study with college athletes demonstrated that balance may be impaired in postconcussive states relative to nonconcussed states.²⁰ The difference between our results could stem from our recruitment methodologies: 1) Our study compared concussed subjects to non-head-injured trauma subjects, rather than healthy athletic controls, and it is conceivable that body or extremity trauma may affect balance, and 2) the athlete study recruited subjects complaining of postconcussive symptoms from a concussion center, rather than regardless of symptoms, as we recruited them, and thus may have identified a more symptomatic subset of concussion patients. Their study thus compared the sickest patients to the most physically well, whereas ours compared two groups of trauma patients.

TABLE 5. SUMMARY STATISTICS FOR SAC SUBSET OF THE SCAT3

<i>SAC total</i>	<i>Observations</i>	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>SD</i>	<i>p value</i>
Non-head-injured	23	20.000	30.000	25.087	2.695	1.000
CT ⁻	39	8.000	29.000	21.872	5.709	0.108
CT ⁺	13	12.000	27.000	20.231	4.902	0.012

SAC, Standardized Assessment of Concussion; SCAT3, Sport Concussion Assessment Tool 3; CT, computed tomography; SD, standard deviation.

TABLE 6. *P* VALUES EVALUATING WHETHER THERE IS A LINEAR RELATIONSHIP BETWEEN EYE-TRACKING METRICS AND SYMPTOM SEVERITY SCORE, AND BETWEEN EYE-TRACKING METRICS AND SAC FROM 75 TRAUMA PATIENTS

Variable	To symptom severity score p value	To SAC p value
Horizontal conjugacy	0.012	0.003
Top	0.291	0.067
Right	0.036	0.010
Bottom	0.012	0.003
Left	0.129	0.061
Vertical conjugacy	0.150	0.082
Top	0.832	0.867
Right	0.018	0.094
Bottom	0.654	0.288
Left	0.053	0.011
Total conjugacy	0.037	0.011

SAC, Standardized Assessment of Concussion.

Balance testing as an outcome measure for concussion may be suboptimal. Baseline balance capability is highly variable among the general population, ranging from trained athletes to sedentary individuals. There is a learning effect associated with balance testing,^{21,22} and, as our data suggest, it is conceivable that body or extremity trauma may also affect balance.

Although it is also possible that there could be a learning effect associated with watching television (the more one watches, the more conjugate the gaze), we have noted that ratios of vertical to horizontal eye movement are increased by increasing mass effect, regardless of video repetition, and that serial watching by subjects with stable neurological disease does not show a learning effect (manuscript in press at *Journal of Neurosurgery*).

There are limitations to our data. In the control subject population, we have relied on self-report for medical and ophthalmic history. Many subjects were hospital employees, research volunteers, colleagues, or friends of the investigative team and may not have been forthcoming about their past medical history, medica-

tions, and drugs used in the day preceding eye-tracking testing. The long-term impact of medications and other agents consumed greater than 1 day before is also unknown. Additionally, not all patients in all comparison groups were on the same concomitantly administered medications. Because keppra is the major medication occurring more commonly in one group than the others, it may potentially contribute to abnormal eye movements in the positive head CT group; however, the negative head CT patients have similar eye movement abnormalities as positive head CT patients, and none of these patients had consumed keppra.

A second limitation arises from the natural incidence of strabismus. In a population of 14,006 consecutive patients examined at a pediatric eye clinic in Rome, 2.72% demonstrated either A- or V-pattern strabismus.²³

In addition to congenital confounders, there may also be conditions leading to acquired disconjugacy, which will yield a false positive with our algorithm. Such disconjugacy may be the result of neurological causes, including hydrocephalus, demyelination, inflammation, infection, degenerative disease, neoplasm/paraneoplastic syndrome, metabolic disease including diabetes, or vascular disruption, such as stroke, hemorrhage, or aneurysm formation. Disconjugacy or vergence disorders may also result from ophthalmologic causes, such as conjunctivitis, ophthalmoplegia, ocular injury, or other thyroid-related orbital dysfunction.

A final limitation of this study is that neither formal optometric nor ophthalmic testing was performed in the trauma setting. Future studies will reveal how an evaluation of eye movements (smooth pursuit, dysmetric saccades, and so on) done by a trained neurological or ophthalmic consultant compares to the eye-tracking device. In addition, cost comparisons of the technology versus an examiner will likely be helpful.

Conclusions

This work describes an objective, rapid, noninvasive, quantitative algorithm for assessment of brain-injured subjects that is not imaging or anatomy based, but rather entirely physiological/functional. When applied to a trauma population, this algorithm reveals that subjects who received a head CT for suspected brain injury

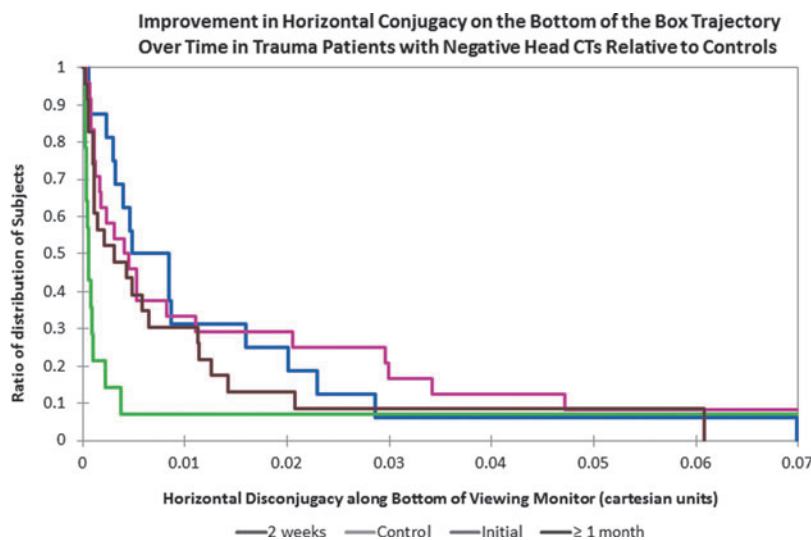


FIG. 3. Bottom segment of the box trajectory's horizontal disconjugacy in nonstructural brain injury improved over time, yet remained statistically significantly different even at 4 weeks postinjury. CT, computed tomography. Color image available online at www.liebertpub.com/neu

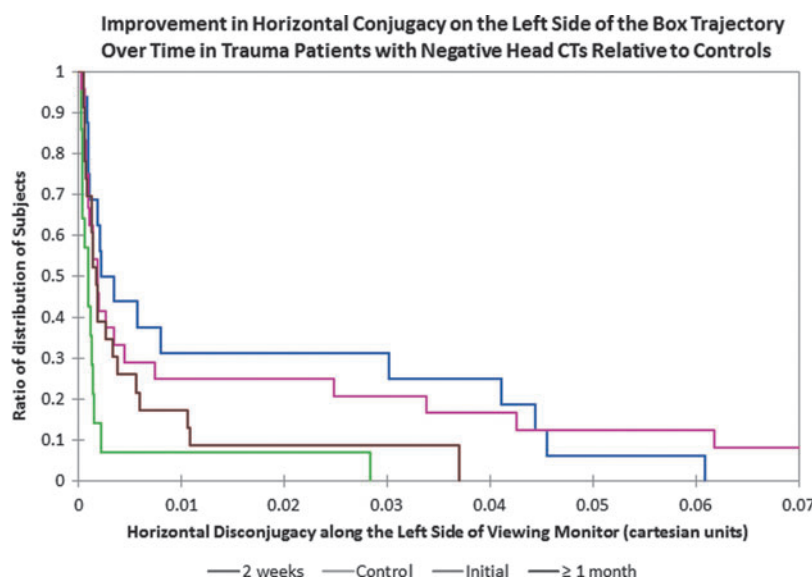


FIG. 4. Left segment of the box trajectory's horizontal disconjugacy in nonstructural brain injury improved over time, and by 4 weeks postinjury, was equal to normal controls. CT, computed tomography. Color image available online at www.liebertpub.com/neu

(test group) or actually had a structural brain injury (positive controls) had significantly greater oculomotor disruption than non-injured controls. Trauma patients with nonhead injuries (negative controls) did not have significant oculomotor disruption. The oculomotor disruption correlated with symptom severity in all trauma patients and improved with time.

Concussion is a condition that has been plagued by lack of clear definition and diagnostics. Establishment of eye tracking as an objective measure would enable testing of prophylactic devices for concussion (e.g., helmets) as well as of therapeutics. It would potentially enable informed decision making regarding return to baseline activity or sport play. In conjunction with devices such as accelerometers and other helmet sensors, eye tracking could be used to identify which impacts render the most disruptive blows and thus should be eliminated by ruling.

The additional significance of this work is its establishment of the utility of nonspatially calibrated eye tracking. Spatial calibration not only requires consistent anatomical function and relative neurointegrity, but also may mask minor deficits. Concussion may be the first of several neurological disorders for which eye tracking will be the preferred diagnostic. Other candidate disorders include hydrocephalus, intracranial hypertension, normal pressure hydro-

cephalus, and neurodegenerative diseases. We will describe eye tracking findings with these conditions in our future work.

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Author Disclosure Statement

Uzma Samadani has submitted two utility patents and three provisional patents describing the technology utilized in this article. These patents are owned by NYU and the VA and licensed to Oculogica Inc., a company cofounded by Uzma Samadani and Robert Ritlop, and in which they have an equity interest.

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TABLE 7. ROC ANALYSIS OF HORIZONTAL CONJUGACY METRICS VERSUS CT READ AS POSITIVE BY RADIOLOGY

Metrics	AUC	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Right	0.750	0.69	0.81	0.43	0.93
Bottom	0.752	0.54	0.92	0.58	0.91
Left	0.728	0.77	0.67	0.32	0.93
Top	0.761	0.62	0.78	0.36	0.91

ROC, receiver operating characteristic; CT, computed tomography; AUC, area under the curve.

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Address correspondence to:
Uzma Samadani, MD, PhD
Department of Neurosurgery
New York University School of Medicine
423 East 23rd Street, MC 112
New York, NY 10012

E-mail: uzma.samadani@nyumc.org