ORIGINAL ARTICLE

Saccadic Eye Movements in Mild Traumatic Brain Injury: A Pilot Study

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ABSTRACT: ***Objective:*** To investigate whether repeat saccadic reaction time (SRT) measurements using a portable saccadometer is useful to monitor patients with mild traumatic brain injury (mTBI). ***Methods:*** Seven patients with newly-diagnosed mTBI and five age-matched controls were prospectively recruited from an Emergency Department. Saccadic eye movements, symptom self-reporting and neuropsychological tests were performed within one week of injury and again at follow-up three weeks post-injury. Control patients underwent saccade recordings at similar intervals. ***Results:*** Median saccade reaction times were significantly prolonged within one week post-injury in mTBI compared to controls. At follow-up assessment there was no significant between-groups difference. Changes in median SRT between the two assessments were not statistically significant. Four of the seven mTBI patients showed significantly increased SRT at follow-up; three of the mTBI patients and all controls showed no significant change. Among the three mTBI patients with persistent decreased SRT, two experienced loss of consciousness and reported the greatest symptoms, while the third was the only subject with significant decrease in neuropsychological testing scores at both assessments. ***Conclusion:*** In three of seven mTBI patients, saccadic eye movements remained delayed within three weeks post-injury. These three patients also showed persistent symptoms or no improvement on neuropsychological testing. This pilot study using a portable saccadometer suggests that comparing SRT from three weeks post-injury to that within one week of injury may be useful for early detection of a subpopulation at risk of persistent disability from mTBI. This finding suggests that further investigation in a large study population is warranted.

RÉSUMÉ: Les saccades oculaires dans le traumatisme cérébral léger : une étude pilote. ***Objectif :*** Le but de l'étude était d'évaluer si les mesures répétées du temps de réaction saccadique (TRS) au moyen d'un saccadomètre portable est utile pour le suivi des patients atteints d'un traumatisme cérébral léger (TCL). ***Méthode :*** Sept patients chez qui un diagnostic de TCL venait d'être posé et 5 sujets témoins appariés pour l'âge ont été recrutés prospectivement au département des urgences. Les saccades oculaires, les symptômes rapportés par le patient et les tests neuropsychologiques ont été documentés dans la semaine suivant le traumatisme et de nouveau au moment du suivi, 3 semaines après le traumatisme. L'enregistrement des saccades chez les patients témoins a été fait aux mêmes intervalles. ***Résultats :*** Les temps médians de réaction saccadique étaient prolongés significativement au cours de la semaine suivant le traumatisme chez les patients ayant subi un TCL par rapport aux témoins. Au moment de l'évaluation de suivi, il n'existait pas de différence significative entre les deux groupes de patients. Les changements dans le TRS médian entre les deux évaluations n'étaient pas significatifs au point de vue statistique. Quatre des 7 patients atteints d'un TCL avaient un TRS augmenté de façon significative au moment du suivi ; aucun changement n'a été observé chez 3 des patients atteints d'un TCL et chez les témoins. Parmi les trois patients atteints d'un TCL qui ont présenté une diminution persistante du TRS, 2 avaient eu une perte de conscience et rapporté les symptômes les plus sévères, alors que le troisième était le seul chez qui une diminution significative des scores aux tests neuropsychologiques lors des deux évaluations avait été notée. ***Conclusion :*** Chez 3 des 7 patients ayant subi un TCL le retard des saccades oculaires persistait 3 semaines après le traumatisme. Ces 3 patients présentaient également des symptômes persistants ou aucune amélioration lors des tests neuropsychologiques. Cette étude pilote effectuée au moyen d'un saccadomètre portable suggère que la comparaison du TRS evalué 3 semaines après le traumatisme à celui fait dans la semaine suivant le traumatisme pourrait être utile pour détecter précocement la sous-population de patients à risque d'invalidité persistante suite à un TCL. Selon nos observations, il serait justifié de procéder à des recherches sur un échantillon de patients plus considérable.

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Mild traumatic brain injury (mTBI) presents a major public health concern worldwide.[1-5] Approximately 10-15% of those who sustain mTBI develop long-term disability with health, psychosocial functioning and quality of life consequences.[6] Currently, there is no consensus regarding the diagnosis and treatment of mTBI,[4,7] and assessment of clinical symptoms and signs and other indicators are not able to predict which patients will develop permanent disability compared to those with a better prognosis. Development of novel biomarkers to predict this high-risk population is critical to improve follow-up and for optimal use of clinical resources. It is therefore essential, from a clinical perspective, that we develop user-friendly, and cost-effective, surrogate markers to detect patients with persistent mTBI.

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Neuroanatomical/neurobiological correlates of mTBI have not yet been completely elucidated. Along with clinical assessment and neuropsychological tests, studies of saccadic eye movements may provide insights into mTBI. Saccades are rapid eye movements that move the line of sight between successive points of fixation.[8,9] Their dynamic properties are well understood and easily measured, including reaction time, amplitude, peak velocity, duration, and frequency of errors.[10] Reaction time, or latency, represents the time interval between presentation of a target and initiation of eye movement.[10] In healthy individuals, reaction times fall within a normal range; alternatively, they may fall within a separate, faster range of reaction times which represents a subpopulation of "early response" saccades.[11] Characteristic variation in saccadic reaction times across trials is a reflection of cortical decision time.[12] Prolonged saccadic reaction times have been observed in various optic nerve pathologies that convey visual signals to the saccade generating network,[13,14] and we have recently shown that saccadic eye movements are delayed in glaucoma, the leading cause of world blindness.[15] Monitoring an individual's saccadic reaction time rate (1/(reaction time)) may also represent an important quantitative approach to assessing the consequences of this form of head injury.[16] Studies in severe TBI with persistent symptoms from a chronic care facility showed persistent prolongation of reaction time.[17] Reflexive saccades have been rarely studied in mTBI patients. An early study showed that the saccade reaction time was not altered in mTBI.[18,19] However, a recent study of amateur boxers showed prolonged reaction time immediately after fight, and progressive shortening with recovery within two weeks after fight.[16] Similarly, reaction time rate was decreased immediately following injury before returning to baseline.[16] Based on these studies, it is not clear whether saccadic reaction time can be used to monitor patients with mTBI to detect those at risk of developing ongoing brain injury. We show here that reflexive saccadic reaction time have potential as a surrogate measure of dysfunction following mTBI in a tertiary care trauma center, and as a biomarker to detect those patients at risk of ongoing evidence of injury from mTBI.

Material and Methods

Participants

Ethics approval was obtained from St. Michael's Hospital Research Ethics Board and all participants gave written informed consent prior to inclusion in the study. Inclusion and exclusion criteria for patients and controls are listed in Table 1.[20-23] Adults greater than 80 years of age were excluded because of aging effects on saccadic reaction times.[24,25] Prior to the start of each assessment, all participants provided a medical history and underwent a screening neurological and eye examination. No participants were taking any medications which are known to directly or indirectly interfere with attention or oculomotor function.[21] Baseline depressive symptoms were evaluated in both groups of participants using the Centre for Epidemiologic Studies Depression Scale (CES-D),[26] as depression may affect saccadic reaction times.[27] The CES-D is well-validated and reliable for screening depressive symptoms in the general population;[26] however, it has also been validated as a sensitive screening tool for major depressive disorders in mild-to-moderate TBI patients.[28,29] There were no significant differences on CES-D scores between mTBI group and controls (Mean± SD=6.57±4.72; 5.40±3.13 , respectively, P=0.64; Table 2), using an independent-samples t-test.

Seven patients (male (n=4); female (n=3)) with newly diagnosed mTBI (Tables 2 and 3) were included in this study. All patients were recruited upon presentation to the hospital's Emergency Department (ED). Mean age was 35 years (range: 18-57 years), and mean duration of education was 15.5 years (range: 12-20 years). Mechanisms of injury included sporting (n=3), occupational (n=2) and accidental (n=2) incidents. Mild TBI was diagnosed clinically by an emergency physician. Mild TBI was defined according to the World Health Organization (WHO) criteria for isolated mTBI:20 Glasgow Coma Scale

Table 1: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Age ≥ 18 years	Age >80 years
Abillity to provide consent	Medically unstable or intoxicated patients
Non-penetrating head impact occurring within 0-7 days of presentation to ED meeting WHO criteria for isolated mTBI[20]	Patients taking psychotropic medications or medications known to interfere with oculomotor function or attention[21]
	Immunocompromised patients (HIV/AIDS or taking immunosuppressive therapy)[22]
OR	History of neurological/neurodegenerative or eye disease[10]
No history of head injury (control subjects)	History of uncontrolled diabetes[23]
Normal or corrected to normal visual acuity of at least 20/50 OU	History of incisional brain or eye surgery
Literacy/adequate English language skills	History of psychiatric illness or substance abuse
Grade 8 education or higher	History of traumatic brain injury (prior to presenting injury)

ED=Emergency Department; WHO=World Health Organization; GCS=Glasgow Coma Scale; LOC=loss of consciousness; PTA=post-traumatic amnesia; OU=both eyes (oculus uterque)

Table 2: Demographics

	Control	mTBI	Significance
Number	5	7	-
% Female	40%	33%	-
Age (Mean ±SD years)	26.60±4.83	35.28±15.35	*P*=0.257
Education (years)	-	15.5±3.68	-
CES-D	5.40±3.13	6.57±4.72	*P*=0.64

Age and education measured in total years. CES-D to detect depression measured as total score. Significance P-values represent the outcome of an independent samples t-test. Years of education not collected for control group (relevant only to neuropsychological testing).

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Table 3: Participant summary data for mTBI patients and controls

Control		
#	Age (yrs)	Gender
1	27	M
2	21	F
3	27	M
4	34	M
5	24	F
mTBI		
#	Age (yrs)	Gender
1	53	M
2	19	F
3	18	M
4	39	M
5	57	F
6	32	M
7	29	F

(GCS) 13-15 after 30 minutes following presentation to ED manifested by at least one of the following symptoms: Loss of consciousness (LOC) ≤ 30 minutes; post-traumatic amnesia (PTA) ≤ 24 hours and/or other transient neurological abnormalities. Participants underwent initial testing within one week of injury (Mean=4 days post-injury, range: three hours -six days), and follow-up testing approximately two weeks later (Mean=16 days post-injury, range: 14-21 days). Timing of assessments was based on the natural history of uncomplicated mTBI, as post-concussive symptoms and neurocognitive function recover within the first ten days following injury.[30-32]

Five age-matched neurologically healthy individuals (Tables 2 and 3) male (n=3); female (n=2)) with no history of eye disease (Mean=27 years, range: 21-34 years) served as a control group. They underwent saccadic eye movement recordings at first and follow-up assessments (Mean interval=12 days; range 6-14 days).

Rivermead Post-Concussion Symptoms Questionnaire (RPSQ)

Participants rated the presence and severity of 16 symptoms commonly experienced following mTBI on the RPSQ.[33-34] The problem-status of symptoms was measured on a scale from 0-4 (0=not experienced at all after the injury, 1=experienced but no more of a problem compared to before the injury, 2=a mild problem, 3=a moderate problem, 4=a severe problem). For both assessments, the assessment period for answers on the RPSQ was extended from 'the previous 24 hours' to 'the time post-injury'. The key measure was the cumulative total of all symptoms.

Neuropsychological Testing

Many studies describe variable sensitivity of neuropsychological testing but identify significant change on Hopkins Verbal Learning Test (HVLT).[35-40] Neuropsychological tests administered to mTBI patients included HVLT-Revised (HVLT-R) Delayed Recall and Discrimination Index. The neuropsychological assessment was completed by a doctoral student (S.J.M.). The student was trained in the administration of neuropsychological testing and closely supervised by a cognitive neuroscientist (T.A.S.).[41] Standardized instructions were followed, and results were compared with normative data.[42]

Eye Movement Recordings

Horizontal displacement of the eye was recorded using noninvasive infrared scleral oculometry by a miniaturized, portable, head-mounted saccadometer (Ober Consulting, Poznan, Poland).[43] Subjects were seated in a room with luminance of 500 cd/m^2 (measured with Minolta Luminance Meter LS-100, Osaka, Japan) at a distance of 1.5 m from a matte white surface. A headpiece containing three low-power lasers that project the target stimuli in front of the subject was applied over the bridge of the nose, eliminating the need for head stabilization. Test stimuli comprised three red high contrast (13cd/m^2) targets subtending 0.1° in diameter at 0°, 10° left and 10° right along the frontal plane at eye level. Viewing and recording were performed binocularly. Calibration was performed before each experiment.

Each experiment consisted of a 10-degree step task in order to evoke "reflexive" saccades initiated as a direct result of the visual stimulus. The data recorded from each experiment was used to determine reaction time, duration, amplitude, peak velocity and direction. Output was sampled at a rate of 1 kHz and linear range was within 7% for up to ±30°(Ober Consulting).[43] Each experimental trial began with a central target (presented during a random fore-period of 500-1000 ms), which was extinguished and followed by the appearance of a peripheral target located 10° randomly to the right or left. The stimuli remained projected until the subject either initiated a saccade, or 2000 ms had elapsed. Experiments lasted 15 minutes during which up to 200 trials were conducted. Instructions were consistent across experiments.

Raw saccadometry data was downloaded to a computer for analysis using LatencyMeter Version 4.9 software (Ober Consulting), which automatically excludes blinks and head movements. Trials with latencies between 50 and 600 ms were analyzed, removing anticipatory saccades (<50 ms) and no response trials (>600 ms).[44-46] If at any assessment, the number of saccade trials was greater than the other, the trials with greater number was trimmed to have the same number of saccades as the assessment with lesser number of saccades. The median reaction time and reaction time rate (1/(reaction time)) were calculated. Responses with reaction times between 50 ms and 100 ms were indicative of express saccades[11,24,25,47-50] and their frequency was counted. Trials representing directional errors were analyzed separately.

Statistical Analyses

Statistical analyses were performed using MATLAB Version 7.1 software (The Mathworks Inc, Natick, MA, USA) and SAS 9.2 (SAS Institute Inc, Cary, NC, USA). We performed two-tailed t-tests to compare the mean of the median reaction times for the mTBI group to the mean of the median reaction times for

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Table 4A: Rivermead Post-Concussion Symptoms Questionnaire (RPSQ) and Hopkins Verbal Learning Test-Revised (HVLT-R) Scores [First Assessment]

mTBI Patients	RPSQ Scores	HVLT-R Total Trials	HVLT-R Delayed Recall	HVLT-R Recognition Index
1	0	26	6	8
2	19	22	5	11
3	9	29	11	10
4	9	25	9	10
5	21	29	9	10
6	19	21	8	8
7	36	28	10	11
Mean	16.14	25.71	8.28	9.71
SD	11.52	2.14	1.25	3.25

Table 4B: Rivermead Post-Concussion Symptoms Questionnaire (RPSQ) and Hopkins Verbal Learning Test-Revised (HVLT-R) Scores [Follow-up Assessment]

mTBI Patients	RPSQ Scores	HVLT-R Total Trials	HVLT-R Delayed Recall	HVLT-R Recognition Index
1	0	25	6	7
2	7	26	12	11
3	7	32	11	11
4	1	27	11	10
5	27	35	12	12
6	9	27	9	11
7	15	31	10	11
Mean	9.43	29	10.14	10.42
SD	9.24	3.69	2.11	1.61
Normative data (Mean ± SD)[36]	-	27.49 ± 4.12	10.24± 1.20	11.15 ±.73
95% Confidence Interval[36]	-	±8.09	±3.47	±2.18

the control group at first and follow-up assessments. We subtracted median reaction time at follow-up from median reaction time at first assessment and used a two-tailed t-test to compare the means of the differences. We used a two-tailed t-test to compare reaction time rate at first assessment to that at follow-up assessment for each mTBI patient and each control participant. (P-values less than or equal to 0.05 were considered statistically significant.) Two-tailed t-tests were used to compare other saccade parameters of the mTBI group to those of the controls.

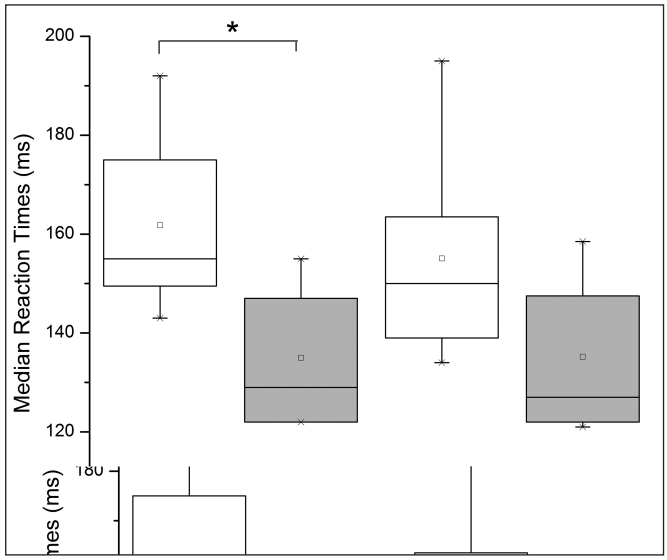

Figure: *Boxplots of median saccade reaction times (ms) at two assessment times. The area marked by an asterisk represents a significant difference in the means of the median reaction times between the mTBI group (161.8±17.4 ms) and the control group (135.0±15.1 ms) at first assessment. At follow-up, the mTBI group shows increased reaction time (155.1±20.5 ms), whereas the control group is stable (135.2±16.9 ms). The difference between the means of the two groups is no longer significant.*

For mTBI patients, neuropsychological test scores were compared to 95% confidence interval of age- and-education-matched normative data, which has been found to be more sensitive than using individualized baseline measures.[42,51]

Results

Three of the seven mTBI patients (#3, #5 and#7) experienced brief loss of consciousness. Mean score from the RPSQ was 16.14 (range: 0-36) at the first assessment following head injury (Tables 4A & 4B). One patient (mTBI #1) reported a score of 0, indicating no symptoms, despite being clinically diagnosed with mTBI. At the follow-up assessment, the mean score on the RPSQ was 9.43 (range 0-27). Two patients (mTBI #5 and mTBI #7) continued to experience significant physical and cognitive symptoms stemming from mTBI, as demonstrated by highest RSPQ scores at the follow-up assessment of mTBI group (RPSQ scores of 27 and 15, respectively). One of the mTBI patients (mTBI #1) who did not present any symptoms (RPSQ scores) showed persistent and significant decrease in HVLT-R recall and recognition indexes (Tables 4A & 4B) at both assessments.

Saccadic Eye Movement Recordings

At the first assessment within one week after injury, median reaction time of the mTBI group was significantly prolonged compared with controls (161.8±17.4 ms vs. 135.0±15.1 ms; *t*-test; P =0.020; Table 5). At the follow-up assessment within three weeks after injury, median reaction time of the mTBI group was prolonged compared with controls but did not reach statistically significant level (155.1±20.5 ms vs. 135.2± 16.9 ms; *t*-test; P =0.106; Table 5). The Figure illustrates the median reaction times in mTBI group and controls during the first and follow-up assessments.

Changes in median reaction time between first and follow-up assessments in mTBI group were not statistically significant

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Table 5: Median reaction time at first and follow-up assessments and t-test results for reaction time rate for mTBI patients and controls

	Reaction Times				*t*-tests[a,b]
	Median of 1st	Median of 2nd	Change 1st-2nd	*Number of trials (n)*	*P*-value
mTBI #1	155.0	150.0	5.0	166	0.113
mTBI #2	149.5	134.0	15.5	124	0.002**
mTBI #3	150.0	139.0	11.0	181	0.003**
mTBI #4	175.0	163.5	11.5	200	<0.001***
mTBI #5	192.0	195.0	-3.0	145	0.409
mTBI #6	168.0	159.0	9.0	197	<0.001***
mTBI #7	143.0	145.0	-2.0	189	0.099
Mean ± SD	161.8 ± 17.4	155.1± 20.5	6.7±7.0		
Control #1	122.0	121.0	1.0	199	0.603
Control #2	155.0	158.5	-3.5	140	0.288
Control #3	122.0	122.0	0.0	199	0.520
Control #4	147.0	147.5	-0.5	200	0.238
Control #5	129.0	127.0	2.0	198	0.752
Mean± SD	135.0± 15.1	135.2± 16.9	–0.2±2.1		
t-tests[b,c]	$t = 2.767$	$t = 1.777$	$t = 0.938$		
	$P = 0.020$*	$P = 0.106$	$P = 0.061$		

[a]These two-tailed t-tests were performed on reaction time rates, i.e., 1/(reaction time). If one assessment was longer than the other, the longer one was trimmed to have the same number of reaction times as the shorter one. [b]Asterisks indicate: * $0.01 < P \leq 0.05$; ** $0.001 < P \leq 0.01$; *** $P \leq 0.001$. [c]These t-tests are two-tailed tests to compare the median reaction times (or change in median reaction times) of the seven mTBI subjects to the median reaction times (or change in median reaction times) of the five controls.

compared to controls (6.7±7.0 ms vs. –0.2±2.1ms, P =0.061, Table 5).

Reaction time rate at follow-up assessment was significantly increased compared to that measured at the first assessment in four of the seven mTBI patients (#2, #3, #4, and #6), while reaction time rate did not show significant change between first and follow-up assessments in three (#1, #5 and #7) of the seven mTBI patients (Table 5). None of the five control subjects showed any significant change in reaction time rate in follow-up assessment compared to that measured at the first assessment. Table 5 shows P-values for each of the mTBI patients and controls.

At the first assessment, among the other saccadic parameters, only frequency of express saccades was significantly decreased in mTBI group compared to controls (2.42±1.84%; 10.18± 5.55%; t-test; P<0.006; Table 6A). The saccadic parameters other than reaction time and reaction time rate did not show significant change at the follow-up assessment within three weeks after injury (Table 6B).

Discussion

In our pilot study, the median reaction times of controls at both initial and follow-up assessments were similar to reported values.[45,52,53]

Complex saccade measurements, such as anti-saccades[19] and memory-population[18,19] have shown saccade alteration in mTBI. Until recently, significant alterations in reflexive saccades have only been demonstrated in severe TBI.[17] Heitger *et al*[54] reported no significant difference in saccadic reaction time measured approximately four to five months following injury, between cases of mTBI with prolonged symptoms and patients who had recovered. Pearson *et al*[16] found saccadic reaction times were delayed in mild TBI in a completely reversible manner following boxing. There are no studies where saccades were measured within three weeks post-injury in mTBI patients who needed acute care in a tertiary care trauma hospital setting. Our pilot data confirms that saccadic reaction times are prolonged in mTBI patients within one week following injury. At the time of the second assessment within three weeks after injury, there was no longer a difference between mTBI patients and controls; this finding was corroborated by an improvement of symptoms in four of the participants. These changes were observed alongside resolving symptom reporting, and scores on neuropsychological testing in most patients. In addition, we demonstrated for the first time that in a significant proportion of patients, saccadic reaction time rate did not show any significant change, and saccades remained delayed at the follow-up assessment within three weeks after injury. No changes in reaction time rates between first and follow-up assessment were detected in controls.

In our study, there was some correlation between saccadic reaction times and self-reporting symptoms, as well as some of the neuropsychological testing results. Three of mTBI patients and all five control participants showed no significant change in reaction time rate. Among these three mTBI patients who had

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Table 6A: Other saccadic parameters at first assessment

Subject ID	Median Duration (ms)	Median Amplitude (°)	Median Peak Velocity (°/ms)	Express Saccades (cum%)	Incorrect Responses (frequency)
mTBI #1	46	9.5	451	1.8	3
mTBI #2	56	13.6	430	2.4	2
mTBI #3	48	9.3	411	6.3	0
mTBI #4	48	9.4	528	1.5	1
mTBI #5	50	9.4	365	1.9	13
mTBI #6	51	10.6	358	0.5	0
mTBI #7	51	9.8	359	2.6	0
Mean	50	10.22	414.57	2.42	2.71
SD	3.21	1.55	62.16	1.84	4.68
C #1	50.3	12.7	448.8	14.1	0
C #2	49.2	10	417.4	0.7	0
C #3	48.6	10.8	443.3	10	0
C #4	49.5	8.6	334.8	14	0
C #5	46	12.5	546.2	12.1	0
Mean	48.72	10.92	438.1	10.18	0
SD	1.63	1.72	75.7	5.55	0
P – value	0.436	0.483	0.567	0.006	0.229

Saccadic parameters (raw values) for injured and control participants on the first assessment. C=control; SD=standard deviation

Table 6B: Other saccadic parameters at follow-up assessment

Subject ID	Median Duration (ms)	Median Amplitude (°)	Median Peak Velocity (°/ms)	Express Saccades (cum%)	Incorrect Responses (frequency)
mTBI #1	47	10.5	430.7	1.8	1
mTBI #2	57	10.7	330.9	8.8	0
mTBI #3	52	9.5	367	9.4	0
mTBI #4	43	9.2	458.2	1.5	0
mTBI #5	46	11.5	457.2	2.1	21
mTBI #6	51	12.5	412	1	0
mTBI #7	49	9.6	349.6	1	0
Mean	49.28	10.5	400.8	3.65	3.14
SD	4.572	1.19	51.87	3.74	7.88
C #1	49	9.9	353.5	11	0
C #2	50	13.5	559.3	1.6	0
C #3	50	12.2	446	14.1	0
C #4	50	8.6	307.9	7.6	2
C #5	42	9.6	559.9	10.2	1
Mean	48.2	10.76	445.32	8.9	0.6
SD	3.49	2.02	115.58	4.69	0.89
P – value	0.666	0.784	0.457	0.056	0.430

Saccadic parameters (raw values) for injured and control participants on the follow-up assessment. C=control; SD=standard deviation

saccadic reaction time rates that remained unchanged, two had persistent highest two RPSQ scores for symptoms at both assessments and were two of three patients with brief loss of consciousness. The third patient (mTBI #1) with lower saccadic reaction time rate at follow-up assessment, showed persistent and significant decrease in HVLT-R recall and recognition indexes, although the patient did not present any symptoms (RPSQ scores). This finding supports the recommendation that symptom questionnaires should not be interpreted in isolation when assessing mTBI, as this often leads to underdiagnosis of traumatic brain injury.[55]

The fact that saccadic parameters such as amplitude, duration and peak velocity were not significantly changed between first and follow-up assessments across mTBI patients suggests that mTBI does not affect the accuracy and motor characteristics of the saccades, but alters the initiation process of saccades.

Relative preservation of express saccades suggests the superior colliculus implicated in express saccades is largely preserved in mTBI cases in this pilot study. This finding is consistent with the findings reported by Heitger and coworkers.[56]

Currently, there are no objective markers to predict which mTBI sufferers will transform to chronic, complicated cases in the mTBI spectrum, despite this occurring in up to 15% of injured patients.[6] In our study, there were three patients (mTBI #1, #5 and #7) whose saccadic reaction time rate did not resolve at the follow-up assessment. Further analysis revealed two of them had the highest symptom load immediately following injury and persistent symptoms at follow-up. They were both among the 3 injured patients who experienced brief loss of consciousness following head injury. One of these patients (mTBI #5) also made a high frequency of incorrect responses during both saccade recordings compared to other participants. Interestingly, both of these patients were female, which has been identified as a risk factor for persistent symptoms.[57,58] While it is not yet clear whether these two patients were developing chronic sequelae from mTBI, these findings suggest that reflexive saccadic latencies may be a useful biomarker to monitor for both recovery and persistent disease. Future research could include serial follow-up assessments in order to identify recovery from mTBI as well as transformation to ongoing mTBI, based on saccadic reaction times alongside more comprehensive neuropsychological measures. Since the neural substrate involved in saccade generation is different from that involved in the tested cognitive functions,[10] detailed neuroimaging studies will be needed to assess structural integrity of the neural pathways involved in saccade generation as well as neuropsychological functions.

There are a number of limitations to our pilot study. The sample size is small, and sample bias cannot be excluded, as our study is comprised of individuals who chose to seek medical attention following mTBI. However, representativeness of sample at the clinical setting of a tertiary care trauma centre, is suggested by age, gender and mechanisms of injury.[59] Although there was no statistically significant difference between mean ages of the experimental and control groups, tighter age-matching between-groups could minimize aging effects on saccadic reaction times.[25] There is often a delay between time of injury and decision to seek medical attention. Individuals were tested at varying time courses of injury, based on time of presentation to Emergency Department. The limitations of neuropsychological testing are well-described[60] and the use of computerized testing may have been able to overcome some of these weaknesses. Finally, saccadometry results as well as

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neuropsychological tests can be affected by variables such as fatigue which may occur independently of injury sequelae.

Conclusion

This pilot study shows for the first time that persistent prolonged saccadic reaction times in mTBI patients may separate patients with persistent mTBI from those with recovering mTBI. These preliminary results support the need for larger multidisciplinary investigation, including neuropsychological and neuroimaging studies, to validate whether saccadic reaction times, measured by a portable head-mounted saccadometer, may serve as a biomarker to monitor mTBI patients, and to detect those at risk of developing persistent mTBI.

Ethical Adherence

Ethics approval was obtained from our institution's Research Ethics Board and all participants gave written informed consent prior to inclusion in the study.

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