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iVOMS: Instrumented Vestibular / Ocular motor screen in healthy controls and mild traumatic brain injury

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ABSTRACT

Objective Vestibular/ocular deficits occur with mild traumatic brain injury (mTBI). The vestibular/ocular motor screening (VOMS) tool is used to assess individuals post-mTBI, which primarily relies upon subjective self-reported symptoms. Instrumenting the VOMS (iVOMS) with technology may allow for more objective assessment post-mTBI, which reflects actual task performance. This study aimed to validate the iVOMS analytically and clinically in mTBI and controls.

Methods Seventy-nine people with sub-acute mTBI (<12 weeks post-injury) and forty-four healthy control participants performed the VOMS whilst wearing a mobile eye-tracking on a one-off visit. People with mTBI were included if they were within 12 weeks of a physician diagnosis. Participants were excluded if they had any musculoskeletal, neurological or sensory deficits which could explain dysfunction. A series of custom-made eye tracking algorithms were used to assess recorded eye-movements.

Results The iVOMS was analytically valid compared to the reference ($ICC_{2,1}$ 0.85–0.99) in mTBI and controls. The iVOMS outcomes were clinically valid as there were significant differences between groups for convergence, vertical saccades, smooth pursuit, vestibular ocular reflex and visual motion sensitivity outcomes. However, there was no significant relationship between iVOMS outcomes and self-reported symptoms.

Conclusion The iVOMS is analytically and clinically valid in mTBI and controls, but further work is required to examine the sensitivity of iVOMS outcomes across the mTBI spectrum. Findings also highlighted that symptom and physiological issue resolution post-mTBI may not coincide and relationships need further examination.

1. Introduction

Mild traumatic brain injury (mTBI), also known as concussion, occurs following a direct or indirect impact to the head or neck causing a complex pathophysiological process and damage to the diffuse tissue [1]. In the UK alone, the government reported that around 1.3 million people per year attend hospital emergency departments for head injury and 75 % of these are mTBI [2]. Signs and symptoms which commonly accompany mTBI include loss of consciousness, dizziness, headache, disorientation, and nausea [3]. It is known that deficits in ocular motor functioning exist post head injury when compared with age matched controls across multiple domains [4]. Diagnosis of mTBI and the neural impairment incurred is typically performed with subjective clinical observation or patient self-report (e.g., Sports Concussion Assessment Tool – 5th version (SCAT-5) [5] and the Rivermead Questionnaire [6]), with very little objective assessment performed, which leads to subtle deficits in function going unnoticed.

Subtle impairment in vestibular (e.g., vertigo, dizziness, unsteadiness / balance issues) or ocular function (e.g., visual acuity, pupillary function, nystagmus, and saccadic eye movement [7]) are common following an mTBI, which is unsurprising considering many of the brain's most vulnerable pathways involve aspects of visual control [8,9]. For example, up to 80 % of concussed athletes report issues with their vision within the first week of their injury [10]. However, these

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impairments are more difficult to detect subjectively than typical self-reported symptoms (e.g. confusion and nausea) and they often persist post-concussion [11]. One tool that is commonly used to evaluate these impairments is the Vestibular / Ocular motor screening (VOMS), which involves a patient performing eye movement tasks of smooth pursuits, saccades, convergence, vestibular ocular reflex (VOR) and visual motion sensitivity (VMS) tasks and reporting their symptoms (i.e., headache, dizziness, nausea and fogginess). While the VOMS has been shown to have some discriminative utility in mTBI, it is at risk for inaccurate diagnosis, as patients can minimize symptoms for personal or external motivations to return to their usual activities [12,13]. There is also no evidence that symptomology during the VOMS tasks relates to specific objectively measured eye movement impairments, which makes rehabilitation and recovery tracking difficult.

There is demand for more objective methods of assessment of eye movements after mTBI in order to assess and monitor these subtle impairments [14], which could impact daily function or lead to increased risk of further injury. Eye tracking has shown promise in detection of subtle deficits that relate to underlying neural impairment in mTBI [15,16]. Specifically, various commercial devices have been developed and marketed that can examine a range of eye movements, such as the EyeBox, EyeSynch, iPAS etc. However, commercial eye tracking systems have a large expense (e.g., EyeBox ~$60k) and the proprietary 'black-box' nature of the algorithms used to derive outcome measures makes it difficult to trust that deficits are accurately being measured. Additionally, many of these commercial systems have received little validation, with most relying on clinical validation (e.g., differentiate groups, show decline or ability to monitor recovery etc.) but none having any analytical validation of underlying algorithms performed (i.e., comparison to accepted references), which is a prerequisite for digital biomarkers with regulatory bodies. Furthermore, many of the eye movement tasks that are performed with commercial systems take a long time (some up to 20 min) to perform and there is no capture of patient feedback (e.g., symptomology during tasks). There is a need to develop quick and clinically feasible eye tracking capabilities for mTBI assessment that does not rely on proprietary algorithms and could be conducted at relatively low cost.

Mobile eye trackers can be easily implemented in clinical environments as they can be quickly deployed, do not require a laboratory or a large amount of space. Furthermore, the cost of mobile eye-tracking devices has substantially reduced in recent years (e.g., Pupil Labs Invisible ~$5k). These systems now support open-source, device agnostic algorithms that can be applied across various devices with the same or similar sampling frequencies. Moreover, many of these systems demand minimal expertise to operate, as calibration is either a single point for patient to view or an automatic process. Mobile eye-trackers can instrument eye movement assessment during standard clinical tests, such as the VOMS (e.g., instrumented VOMS (iVOMS)), which would combine objective measurement with subjective patient reporting of symptoms. The combination of self-reported symptoms and objective eye movement outcomes would also provide a unique ability to examine whether symptoms reported during the VOMS actually relate to objectively measured eye movement deficits, as this has not been shown previously. Development and validation (both analytical and clinical validation) of an iVOMS assessment for mTBI would allow clinicians to obtain objective and subjective feedback on eye movement deficits, which could be done quickly in any location and with little technical eye-tracker expertise.

This study aimed to perform; 1) Analytical validation of the iVOMS: Several algorithms were developed to instrument the various eye movement tasks of the VOMS (iVOMS) and the eye movement outcomes were compared to the reference of manual observation of videos ('reference standard') in the assessment of individuals with mTBI (<12 weeks post-injury) and healthy controls, in line with previous analytical validation work [17,18]; and 2) Clinical Validation of the iVOMS: This was performed through examination of whether there were significant differences in iVOMS outcomes between those with mTBI (<12 weeks post-injury) and healthy controls, and via correlation of iVOMS outcomes with traditional subjective measures of symptom severity (e.g., VOMS and SCAT5). We hypothesised that the algorithms developed for the iVOMS would have good analytical validation compared to reference methods, and good clinical validity with the ability to differentiate mTBI from healthy controls and correlation to typical symptom scales.

2. Methods

This study is part of a larger study on assessing and providing rehabilitation of balance following mTBI. The following section is a brief overview of the study methodology. For detailed information, please refer to the published protocol [19].

2.1. Participants

A total of 79 people with sub-acute mTBI and 44 healthy controls (convenience sample) were enrolled and tested. Data were collected at two independent research sites: Oregon Health & Science University (OHSU) and Northumbria University (NU). Seventy-nine (79) individuals with mTBI and 10 healthy controls were recruited as part of a larger study at OHSU (ClinicalTrials.gov identifier: NCT03479541), while 34 additional healthy controls were recruited at NU (ClinicalTrials.gov identifier: NCT04938570) [20]. For OHSU, approval of the study was granted through a joint institutional review board from OHSU and Veterans Affairs Portland Health Care System (VAPORHCS) (IRD #17,370). At NU, the study was approved by the university research ethics committee (REF #2365). Written informed consent was obtained from participants prior to all testing.

2.1.1. Inclusion/exclusion criteria

Participants with mTBI were included if they had a physician confirmed diagnosis of mTBI within 12 weeks of their injury; if they were aged between 18 and 60 years old; endorsed ≥1 for either balance, dizziness nausea, headache, or vision AND had a minimum total symptom severity score of 15 on the graded symptom checklist from the SCAT – Version 5; and having no or minimal cognitive impairment (≤9 on the Short-blessed test).

All participants (mTBI and healthy control) were excluded if they had any other musculoskeletal, neurological, or sensory deficits that could explain dysfunction; healthy control participants were excluded if they had a previous mTBI, had a moderate to severe substance use disorder within the past month; if they experienced severe pain during the evaluation (≥7/10 subjective visual analogue scale rating); if they were pregnant; if they were unable to abstain from medications that might impair balance 24 h prior to testing; had contraindications to rehabilitation such as unstable Cervical Spine; and if they actively participated in physical therapy for their mTBI. In line with previous research, mTBIs were categorised as immediate (between 0 and 7 days), acute (within 1–6 weeks), post-acute (7–12 weeks), and >12 weeks as chronic mTBI [19,21].

2.2. Equipment

Infra-red (IR) mobile eye-tracker: A head-mounted infra-red mobile eye-tracking system - Tobii Pro Glasses 2 (100 Hertz (Hz), Tobii Technology Inc., VA, USA) recorded participant eye-movements during the VOMS [22]. Participant pupils were recorded binocularly by means of four infrared illumination eye cameras, which provided the gaze coordinates (x, y). The Tobii system also contains tri-axial accelerometer and gyroscope for measuring head kinematics (sampled at 100 Hz).

Video: The infrared (IR) eye-tracker used a dual camera view system, with a video recording from an eye camera and a field of view camera (1080p high definition, 50 Hz). The eye-tracker was calibrated prior to data collection using the manufacturer's single point calibration

method, which overlaid the eye and field video outputs with a crosshair provided on the video to represent pupil location. Coordinate (*x, y*) data were derived from the cross-hair (red circle) location and were used to derive eye-movements.

2.3. Protocol

All eligible participants gave informed consent after the initial screening. Demographics, and mTBI symptoms (SCAT5 symptom score) were recorded. SCAT5 symptoms were reported prior to the initiation of the VOMS. At both sites, testing was conducted while participants wore the Tobii Pro glasses. They were asked to perform the VOMS [10] tasks, with a 3-second pause at the start and end of each test to allow the eye tracker to reset. Symptoms were scored on a scale of 0 (none) to 10 (worst) after each of the following tasks: 1) horizontal and vertical smooth pursuit, 2) horizontal saccades, 3) vertical saccades, 4) near point convergence, 5) horizontal VOR, 6) vertical VOR, and 7) (VMS) (Fig. 1, Table 1). The VOMS is a sensitive tool for mTBI assessment and demonstrates internal consistency [10,23,24].

Smooth Pursuit: Participants were asked to focus on a target approximately 3 feet away and follow it with their eyes (while keeping their head stationary) as it moved horizontally from left to right and vertically up and down (i.e., 1.5 feet to left and right, up and down).

Saccades: Participants were seated and positioned 3 ft from a wall and were asked to move their eyes as quick as possible between two points on the wall separated by 3 ft distance between them (i.e., 1.5 feet either side, up and down). One trial was run horizontally, and another vertically. As per the original VOMS instructions we used 'two points' to move the eyes between, but to ensure consistent distance and approach we did not use fingertips (as per VOMS instructions example).

Convergence: Participants were given a wooden lollypop (i.e., popsicle) tongue depressor stick to hold at arm's length in front of them. A printed letter A (with a size 14-point, black font on white paper) was attached to the top of the lollypop stick. The participants were instructed to slowly bring the stick toward their nose while keeping focus on the letter A, and to stop once they lost focus and started to see double (there were two A's in their vision). Abnormal convergence (in this case from the nose to where they see a double image) was defined as being >5 centimetres (cm) from the nose [10].

Vestibular Ocular Reflex (VOR): This was measured horizontally and vertically by asking the participants to rotate their head while maintaining focus on a still target in the centre of their gaze. Participants moved their head at an amplitude of 20 degrees (°) to each side in time with a metronome set to 180 beats/minute. Ten repetitions from left to right or up and down were performed.

Visual Motion Sensitivity (VMS): The participants were asked to hold out their arms in front of them and link their hands together. They focused on their thumbs and rotated their trunk, head, and eyes as a unit at an amplitude of 80° to the right and left. A metronome was played at 50 beats/minute, and participants were asked to maintain their rotations at the speed of the metronome. Five rotations left and right were performed.

Table 1
Participant demographics and VOMS scores.

	mTBI (n = 79) Mean (SD)	Control (n = 44) Mean (SD)	p
Age (years)	33.91 (11.90)	21.80 (3.83)	**<0.001***
Sex	M (15) / F (65)	M (34) / F (10)	**<0.001***
Height (m)	1.68 (0.09)	1.78 (0.10)	**<0.001***
Mass (kg)	72.03 (13.83)	90.70 (18.61)	**<0.001***
SCAT 5 Symptom Score total	56.42 (20.64)	–	–
Days since injury	33. 87 (21.75)	–	–
VOMS Baseline Symptom Score - total	8.74 (5.27)	0.00 (0.00)	**<0.001***
VOMS Smooth Pursuit Symptom Score - total	8.98 (5.46)	0.59 (2.18)	**<0.001***
VOMS Saccade (horizontal) Symptom Score - total	2.63 (2.21)	0.80 (3.43)	**.006***
VOMS Saccade (vertical) Symptom Score - total	10.81 (6.09)	0.86 (4.28)	**<0.001***
VOMS Convergence Distance (cm)	8.42 (6.20)	4.36 (3.10)	**<0.001***
VOMS Convergence Symptom Score - total	11.10 (6.42)	1.30 (2.54)	**<0.001***
VOMS VOR (horizontal) Symptom Score - total	11.86 (6.70)	1.14 (3.32)	**<0.001***
VOMS VOR (vertical) Symptom Score - total	11.64 (6.22)	1.68 (4.68)	**<0.001***
VOMS VMS Symptom Score - total	12.08 (6.38)	0.00 (0.00)	**<0.001***

[*$p \leq 0.01$, SCAT= Sports Concussion Assessment Tool 5 VOMS = Vestibular/Ocular motor screen, VOR = Vestibular ocular reflex, VMS= Visual motion sensitivity].

SCAT5 Symptom Index: Along with demographic characteristics (i.e., age, height, weight etc.) the symptom index section of the SCAT5 was also collected from the participants [5], as well as self-reported days since injury. The SCAT5 symptoms score involves a self-report of 22 symptoms (e.g., headache, confusion, drowsiness) scored on a 7-point Likert scale. Symptoms are categorised from 0 (none) to 6 (severe), making the highest possible total symptom 132.

2.4. Algorithmic detection of visual events

To analyse data from the eye-tracker, we developed our previous mobile eye-tracker algorithms for saccade detection [17] to provide additional outcomes from other visual tests included in the VOMS. We processed all eye movement data in MATLAB® 2018b (Mathworks, Natick, MA, USA). We initially calculated the frame-to-frame position change of the *x* and *y* co-ordinates of the eye location for each frame in the raw data, which provided a distance in pixels. This distance was then

Smooth pursuit is the ability to follow a slow-moving target.

Saccades are the quick horizontal or vertical eye movements between targets.

Convergence is the ability to view a near target without experiencing double vision.

VOR is the ability to maintain stable vision whilst the head is moving.

VMS is the ability to inhibit vestibular-induced eye movements using vision.

Fig. 1. VOMS outcomes explanation.

converted to degrees using a conversion value (number of pixels on x and y axis divided by degrees of camera field of view). From the change in distance, we calculated the velocity and acceleration of the signal. The specific event detection elements of each algorithm involved the following criteria and outcomes:

1. ***Saccades:*** Pupil velocity >150°/second (~2° distance; to ensure rule out of micro-saccades), acceleration >3000°/s^2, and maximum 100 milliseconds (ms) duration classified a saccade. A gap of >100 ms between eye movements classified a different saccade.
2. ***Smooth Pursuit:*** Velocity >20°/s (maximum 100°/s) and duration >60 ms classified a smooth pursuit. A gap of >100 ms between eye movements classified a different smooth pursuit. Saccadic intrusions (i.e., poor performance) were calculated with the same criteria as above, and saccadic data was removed from smooth pursuits.
3. ***Convergence:*** Velocity >0.5 millimetres/second (mm/s) and >20 mm/s^2 acceleration for both left and right eye combined classified a convergence eye movement. Distance was calculated in mm (of pupil movement) rather than degrees in order to match to the traditional measurement in cm (of eye to target distance). Saccadic intrusions were calculated with the same criteria as above.
4. ***VOR:*** Calculated separately for the horizontal and vertical directions. Saccadic intrusions were calculated with the same criteria as above. After removing saccade data, cross correlation coefficients were used to calculate gain (i.e., similarity between head and eye movement) by examining the relationship between eye tracker head accelerometer data and eye movement x and y co-ordinate data.
5. ***VMS:*** Conducted in the same manner as VOR analysis but only one direction/trial.

2.5. Validation of iVOMS algorithms

Initial validation of the iVOMS algorithm outcomes was performed in a sub-group of participants ($n = 10$ mTBI and $n = 10$ healthy controls). This involved comparing the algorithm output with manual inspection / analysis of the eye-tracking videos by an expert rater [22,25,26].

Video inspection ('reference standard'): Videos were manually analysed in line with previous work [17,18,27]. To compare eye-tracker algorithm results, all high-definition field camera videos were visually inspected by a single expert examiner. This was completed by evaluating the footage frame-by-frame for each participant for each of the VOMS trials (140 videos in total). The visual inspection involved recording the number of saccadic events (fast eye-movements) seen within each video, which was then compared to the saccade events determined by the IR eye-tracker algorithm output.

2.6. Statistical analysis

Data were analysed using SPSS (v28, IBM Inc, IL, USA). Normal data distribution was determined using Kolmogorov-Smirnov tests. Demographics were reported using descriptive statistics (means, standard deviation etc.), with group differences calculated using independent *t*-tests and chi squared tests when appropriate.

2.6.1. Analytical validity analysis

Algorithm outcomes were compared to manual video analysis by an expert rater (gold-standard or ground truth reference) in line with previous research studies [17,18,27]. Eye movement (e.g., saccade or smooth pursuit) detection (number) was evaluated during all the VOMS tasks, except convergence. Absolute agreement between methodologies was assessed using intra-class correlations ($ICC_{2,1}$). ICCs were interpreted as; poor <0.5, moderate 0.50–0.75, good 0.75–0.90 and excellent >0.90 [28]. Convergence distance was compared between the standard VOMS (distance of target to the nose in cm) and eye-tracker outcomes (distance of pupil movement in mm) using Spearman's correlation coefficients (due to the smaller sub-group sample size).

2.6.2. Clinical validity analysis

To compare eye-tracker outcomes from the iVOMS test between groups, we used one-way ANCOVA with group (mTBI or healthy control) as a between-subject factor, and age and sex as control variables (due to these demographics being significantly different between groups and having known influence on eye-movements and mTBI). Pearson's correlations were used to examine the relationship between iVOMS outcomes that were significantly different between groups(mTBI vs control) and symptom severity measures (VOMS, SCAT5). Control for multiple-comparisons was done with a more stringent p-value of $p \leq 0.01$ (adjusted-alpha = 1 %) to reduce type I error (i.e., detecting a false positive) while attempting to avoid type II error (i.e., failing to detect a true difference) in this exploratory / novel study [29,30].

3. Results

Table 1 shows that the participant groups were significantly different in terms of age, sex, height, and weight (all $p<.001$). The mTBI group also reported significantly worse symptoms on all of the VOMS self-reported symptoms scores and tasks compared to healthy controls (Table 1).

3.1. iVOMS analytical validation

There was good to excellent agreement between the ground truth manual video inspection of saccades and the automated algorithm output (Tables 2 and 3). Specifically, the iVOMS outcomes ranged from good (ICC 0.85) to excellent (ICC 0.99) agreement across the mTBI and healthy control groups for saccade, smooth pursuit, VOR and VMS tasks. Additionally, the VOMS convergence target distance measurement was significantly correlated with the iVOMS pupil distance across groups (mTBI, healthy control) (all $p<.001$).

3.2. iVOMS clinical validation

After adjusting for age and sex within an ANCOVA and applying a more stringent p-value of $p<.01$, there were several significantly

Table 2
Eye movement detection validity.

(50 Hz) Mean n (100 Hz) Mean n	Algorithm ICC (2,1)	Video		
mTBI (n = 10)	SH	19	19	0.92 (0.71 – 0.98)
	SV	20	19	0.91 (0.65 – 0.98)
	SP - saccades	12	10	0.88 (0.48 – 0.97)
	SP	6	6	0.92 (0.68 – 0.98)
	VORH - saccades	12	10	0.85 (0.31 – 0.96)
	VORV - saccades	12	11	0.95 (0.81 – 0.99)
	VMS - saccades	49	48	0.99 (0.98 – 0.99)
Healthy Control (n = 10)	SH	31	32	0.98 (0.91 – 0.99)
	SV	40	39	0.99 (0.97 – 0.99)
	SP - saccades	22	22	0.98 (0.92 – 0.99)
	SP	9	10	0.91 (0.65 – 0.98)
	VORH - saccades	28	25	0.96 (0.63 – 0.99)
	VORV - saccades	26	24	0.98 (0.81 – 0.99)
	VMS - saccades	56	53	0.99 (0.85 – 0.99)
All (n = 20)	SH	25	25	0.98 (0.95 - 0.99)
	SV	30	29	0.98 (0.95 - 0.99)
	SP - saccades	17	16	0.96 (0.91 - 0.99)
	SP	8	8	0.86 (0.71 - 0.95)
	VORH - saccades	20	17	0.97 (0.83 - 0.99)
	VORV - saccades	19	18	0.98 (0.93 - 0.99)
	VMS - saccades	52	50	0.99 (0.97 - 0.99)

[mTBI = mild traumatic brain injury, ICC = Intra-class correlation coefficient, SH = Saccades horizontal, SV = Saccades Vertical, SP = Smooth Pursuit, VORH = Vestibular ocular Reflex Horizontal, VORV = Vestibular Ocular Reflex Vertical, VMS = Visual Motion Sensitivity].

Table 3
Convergence measurement validity.

	VOMS target distance cm	Algorithm pupil movement mm	Spearman's rho
mTBI (n = 10)	8.60	0.74	**−0.92 (p<.001)** *
Healthy Control (n = 10)	4.77	1.81	**−0.89 (p<.001)** *
All (n = 20)	6.69	1.27	**−0.92 (p<.001)** *

[*$p \leq 0.01$].

different variables between the groups and several trends for significance in other variables (Table 4). The iVOMS outcomes showed that vertical saccade duration, velocity, and distance, as well as smooth pursuit velocity and convergence duration were significantly impaired in mTBI compared to healthy controls. There were no outcome measures that had significant differences between groups for the horizontal saccade test of the iVOMS (Table 4). Smooth pursuit mean velocity was significantly lower in mTBI than controls (p=.001), and the number of saccadic intrusions and saccadic intrusion number during smooth pursuits were reduced in mTBI compared to controls ($F = 5.75$, p=.001, $F = 5.63$, p=.001 respectively, see Table 4). Additionally, during horizontal VOR (VORH) saccadic intrusion velocity (mean and max) and duration were lower in mTBI compared to controls ($F = 6.17$, $p < .001$, $F = 10.05$, $p < .001$ respectively). Similarly, VORH distance was reduced in mTBI ($F = 10.56$, $p < .001$). During vertical VOR (VORV) significant differences were seen for saccadic intrusion number ($F = 7.28$, $p < .001$). During VMS saccadic intrusion velocity (mean and max) were also reduced in mTBI compared to controls ($F = 6.17$, $p < .001$, $F = 10.05$, $p < .001$ respectively). Convergence duration was also significantly longer in mTBI compared to controls ($F = 36.49$, $p < .001$).

Tables 5 and 6 illustrate the lack of statistically significant relationship between significantly different iVOMS outcomes between mTBI ($n = 79$) and HCs ($n = 44$) and self-reported VOMS symptoms and SCAT5 symptom scores in the mTBI group. However, there were several trends for relationships, such as saccadic intrusion number during VORV with VOMS (r=−0.25, p=.035; Table 5) and mean smooth pursuit velocity with SCAT5 symptoms score ($r = 0.244$, p=.040; Table 6).

4. Discussion

This is the first study to instrument the VOMS with a mobile eye-tracker and perform analytical and clinical validation of the developed iVOMS assessment. This is fundamental in ensuring accurate eye movement outcomes and developing automated data analysis methods that can be used to make clinical decisions in a timely manner. Our study had three key findings. First, mobile eye-tracking and the algorithms used to instrument the VOMS are robust. Second, the iVOMS objective eye movement outcomes can differentiate mTBI from healthy controls in some key measurements. And third, the iVOMS outcomes did not correlate with self-reported symptom severity scores in mTBI (total VOMS and total SCAT5). These findings suggest that mTBI impacts eye movements and highlight the value of adding objective (quantitative) measures for improved mTBI assessment, which can overcome the limitations of self-reported assessment. Conducted in conjunction with subjective measures, the iVOMS can provide a much more comprehensive assessment for mTBI.

4.1. Analytical validation of iVOMS

In accordance with our previous research [17,18,27], we conducted

Table 4
Eye-tracker outcomes from iVOMS.

Mean (SD)			mTBI Healthy Control	
Mean (SD)	*F*	*P*		
SH – Duration (s)	0.03 (0.01)	0.02 (0.01)	3.571	.016
SH – Mean Velocity (°/s)	421.38 (62.94)	434.63 (82.03)	1.630	.187
SH – Max Velocity (°/s)	600.27 (69.91)	600.10 (76.20)	.940	.242
SH – Distance (°)	15.29 (4.61)	14.81 (4.73)	.596	.619
SV – Duration (s)	0.04 (0.01)	0.03 (0.01)	5.097	**.002***
SV – Mean Velocity (°/s)	422.18 (72.39)	469.98 (112.59)	5.480	**.002***
SV – Max Velocity (°/s)	589.64 (85.36)	642.67 (122.31)	4.637	**.004***
SV – Distance (°)	17.13 (6.55)	18.06 (7.54)	4.637	**.004***
SP – Saccadic Intrusion Number	10.99 (7.84)	13.42 (8.89)	**5.749**	**.001***
SP – Saccadic Intrusion Duration (s)	0.04 (0.01)	0.03 (0.01)	1.169	.325
SP – Saccadic Intrusion Mean Velocity (°/s)	454.61 (80.31)	501.53 (65.68)	3.680	.014
SP – Saccadic Intrusion Max Velocity (°/s)	549.21 (103.31)	691.75 (57.52)	1.977	.122
SP – Saccadic Intrusion Distance (°)	8.33 (2.02)	9.05 (1.90)	2.540	.060
SP – Duration (s)	1.48 (1.06)	1.19 (0.51)	1.439	.236
SP – Mean Velocity (°/s)	22.34 (5.31)	25.58 (3.99)	**5.630**	**.001***
SP - Max Velocity (°/s)	85.64 (14.06)	91.61 (5.73)	5.283	**.002***
SP – Distance (°)	35.23 (33.75)	31.49 (16.75)	.320	.811
VORH – Saccadic Intrusion Number	13.00 (6.76)	14.54 (9.36)	1.054	.372
VORH – Saccadic Intrusion Duration (s)	0.04 (0.02)	0.05 (0.02)	1.345	.264
VORH – Saccadic Intrusion Mean Velocity (°/s)	320.20 (95.38)	422.56 (126.32)	**8.996**	**<0.001***
VORH – Saccadic Intrusion Max Velocity (°/s)	494.20 (144.45)	631. 98 (165.05)	**8.389**	**<0.001***
VORH – Saccadic Intrusion Distance (°)	9.48 (3.05)	15.11 (7.93)	**10.559**	**<0.001***
VORH - Gain	−0.01 (0.19)	0.00 (0.12)	.837	.477
VORV – Saccadic Intrusion Number	10.67 (6.16)	17.26 (10.16)	**7.280**	**<0.001***
VORV – Saccadic Intrusion Duration (s)	0.03 (0.01)	0.03 (0.01)	1.837	.145
VORV – Saccadic Intrusion Mean Velocity (°/s)	353.12 (96.13)	356.03 (68.21)	.343	.794
VORV – Saccadic Intrusion Max Velocity (°/s)	457.80 (128.77)	480.37 (103.16)	.401	.753
VORV – Saccadic Intrusion Distance (°)	9.85 (3.28)	12.02 (4.74)	3.475	.019
VORV - Gain	−0.01 (0.12)	0.02 (0.09)	.785	.505
VMS – Saccadic Intrusion Number	26.66 (16.33)	29.55 (20.35)	3.604	.016
VMS – Saccadic Intrusion Duration (s)	0.03 (0.01)	0.04 (0.02)	4.524	**.005***
VMS – Saccadic Intrusion Mean Velocity (°/s)	354.84 (58.32)	401.71 (63.44)	**6.171**	**<0.001***
VMS – Saccadic Intrusion Max Velocity (°/s)	453.33 (90.76)	555.19 (103.58)	**10.046**	**<0.001***
VMS – Saccadic Intrusion Distance (°)	10.41 (2.56)	11.36 (2.20)	1.390	.250
VMS - Gain	0.08 (0.23)	0.01 (0.13)	1.786	.154
Convergence – Timing (s)	0.20 (0.18)	0.24 (0.20)	.998	.396

(*continued on next page*)

Table 4 (*continued*)

Mean (SD)			mTBI Healthy Control	
Mean (SD)	*F*	*P*		
Convergence – Duration (s)	7.37 (2.04)	3.77 (1.56)	**36.486**	**<0.001***
Convergence – Mean Velocity (mm/s)	0.14 (0.07)	0.20 (0.13)	2.681	.050
Convergence – Max Velocity (mm/s)	4.77 (1.83)	4.95 (2.19)	.530	.663
Convergence – Distance (mm)	1.00 (0.52)	0.75 (0.56)	3.255	.024

[*$p \leq 0.01$, SH = Saccades horizontal, SV = Saccades Vertical, SP = Smooth Pursuit, VORH = Vestibular ocular Reflex Horizontal, VORV = Vestibular Ocular Reflex Vertical, VMS = Visual Motion Sensitivity].

Table 5
Relationship between self-reported symptoms during VOMS and iVOMS outcomes in mTBI.

iVOMS outcomes impacted by mTBI	VOMS total symptoms score correlation – r (p)
SP – Saccadic Intrusion Saccade Number (°/s)	−0.172 (0.148)
SP – Mean Velocity (°/s)	0.10 (0.384)
VORH – Saccadic Intrusion Mean Velocity (°/s)	−0.05 (0.688)
VORH – Saccadic Intrusion Max Velocity (°/s)	0.05 (0.673)
VORH – Saccadic Intrusion Distance (°)	−0.00 (0.976)
VORV – Saccadic Intrusion Number	−0.25 (0.035)
VMS – Saccadic Intrusion Mean Velocity (°/s)	−0.05 (0.669)
VMS – Saccadic Intrusion Max Velocity (°/s)	−0.12 (0.311)
Convergence – Duration (s)	−0.07 (0.582)

[*$p \leq 0.01$, SH = Saccades horizontal, SV = Saccades Vertical, SP = Smooth Pursuit, VORH = Vestibular ocular Reflex Horizontal, VORV = Vestibular Ocular Reflex Vertical, VMS = Visual Motion Sensitivity].

Table 6
Relationship between SCAT5 Symptom score and significant iVOMS eye tracking outcomes in mTBI group.

iVOMS outcomes impacted by mTBI	Pearson's correlation - r (p)
SP – Saccadic Intrusion Saccade Number (°/s)	.037 (0.762)
SP – Mean Velocity (°/s)	.244 (0.040)
VORH – Saccadic Intrusion Mean Velocity (°/s)	−0.070 (0.585)
VORH – Saccadic Intrusion Max Velocity (°/s)	−0.017 (0.896)
VORH – Saccadic Intrusion Distance (°)	−0.113 (0.374)
VORV – Saccadic Intrusion Number	.073 (0.572)
VMS – Saccadic Intrusion Mean Velocity (°/s)	−0.165 (0.167)
VMS – Saccadic Intrusion Max Velocity (°/s)	−0.129 (0.279)
Convergence – Duration (s)	.133 (0.252)

[*$p \leq 0.01$, SH = Saccades horizontal, SV = Saccades Vertical, SP = Smooth Pursuit, VORH = Vestibular ocular Reflex Horizontal, VORV = Vestibular Ocular Reflex Vertical, VMS = Visual Motion Sensitivity].

a comparison of algorithmic output to frame-by-frame manual video inspection by an expert rater to validate the data analysis process. The purpose was to determine the robustness of the iVOMS algorithms for eye-tracker accuracy in both individuals with mTBI and healthy controls who performed identical VOMS eye movement tasks. The same fixed algorithms (and settings) were used for both groups and were then compared to manual visual inspection. Our findings showed that the iVOMS algorithms were robust, with good (ICC >0.85–0.9) to excellent (ICC >0.9) agreement for eye movement detection, including saccadic, smooth pursuit, VOR and VMS tests. Eye movement and ruler measured viewing distance during convergence also had excellent correlation (Spearman's rho >0.9) as well. This level of accuracy using velocity-based algorithms for eye movement event detection is consistent with our previous work in mTBI and other neurological groups [16,25,31,32]. The agreement between the ground truth manual video inspection (or ruler measurement for convergence) and the algorithms was similar across the mTBI and control groups during all of the VOMS testing, indicating that the algorithms were robust in detecting eye movement events in both groups and across conditions.

4.2. Clinical validation of iVOMS

Initial clinical validation of iVOMS was shown through the significant differences in some objectively measured eye movement outcomes between mTBI and healthy controls during the iVOMS. Results are in line with literature that has shown impairment in saccadic, smooth pursuit and other eye movements in those with mTBI (from acute to chronic) compared to controls [16]. Specifically, for the iVOMS core outcomes, people with mTBI had significantly slower, longer, and shorter vertical saccades, slower smooth pursuits and longer duration convergence eye movements compared to controls. Saccades and smooth pursuit eye movements have been extensively studied and deficits have been recorded on strictly controlled tasks, with many digital technologies developed to objectively assess these eye movements (e.g., Right Eye, Sync Think, Eye Box etc.) [33–36]. However, this is the first study to show that instrumenting objective eye movement assessment using a mobile eye-tracker is possible during a standard clinical examination, which reduces patient burden (i.e., reduced time of assessment, only complete a single set of tasks, comfortable equipment without complex computerised tasks to complete).

Convergence is the only element of the standard clinical VOMS assessment that provides a quantitative outcome rather than subjective self-reported symptoms (e.g., ruler measured distance of target to nose). Consistent with previous research, convergence eye movements were significantly impaired in our mTBI cohort compared to controls on clinical VOMS measurement (i.e., >5 cm from nose to target in mTBI) [37]. However, there was only a trend for reduced eye movement distance in eye-tracker measured convergence distance data. Nevertheless, eye-tracker data showed that convergence measurement was significantly longer in mTBI, which would not be possible to measure accurately without eye-tracking technology (i.e., the start of eye movement to the end of convergence movement). Our findings highlight that objective monitoring with a mobile eye-tracker may provide insight into subtle deficits that are not usually observed during VOMS assessment in mTBI, which could be a useful addition to traditional clinical examination.

Most group differences related to saccadic intrusions (eye movement errors) during smooth pursuit, horizontal and vertical VOR, and VMS tests. Previous studies have reported that error rates on attentional inhibition tasks and saccadic intrusions during strictly controlled smooth pursuit tasks (i.e., virtual reality headset or rotary chair tasks) can be greater in mTBI compared to control [38]. This suggests we should expect to see a greater number of saccadic intrusion (errors in performance) in our mTBI results [39]. In contrast, our results support findings of greater motor inhibitory control mechanisms in acute and chronic mTBI compared to controls [40–42], as we unexpectedly found that there were significantly less saccadic intrusions in mTBI during smooth pursuits and vertical VOR tasks compared to controls. This may indicate more conservative task performance in mTBI with greater inhibition (i.e., controls completed smooth pursuits quicker than mTBI and did not need to devote task focus, unlike mTBI). This is further supported by mTBI saccadic intrusions being smaller and slower than the controls. Stricter control of eye movements during the prescribed tasks may be related to those with mTBI attempting to hide symptoms or deficits, which has been shown to occur in various mTBI cohorts [43–45].

We observed a lack of significant relationships between subjective self-reported VOMS symptom scores (total score), SCAT5 symptom

scores (total score), and the objectively measured iVOMS outcomes. While the VOMS (and SCAT5) provide information of subjective self-reported symptoms, they do not provide objective measures of eye movements. Therefore, we do not know whether impairment of eye movements during the VOMS actually lead to the symptoms reported. The lack of correlation needs to be examined within future studies, but likely relates to symptom resolution and physiological deficit resolution being distinct within mTBI, with the VOMS self-reported symptoms potentially not reflecting performance on the vestibular/ocular tests being conducted. It is likely that iVOMS deficits may not relate to self-reported symptoms due to other underlying physiological problems interfering with symptomology that cannot be directly measured, such as autonomic or somatic dysfunction [46]. Furthermore, previous studies have shown that even when self-reported symptoms following mTBI are reportedly resolved, patients often still have physiological issues. For example, patients that have self-reported symptom resolution may return to usual activities, but are at high risk of secondary mTBI, musculoskeletal injury or have persistent sensory, motor, or cognitive issues, which highlights that underlying neuro-physiology is not recovered [47–50]. Additionally, there are known limitations of self-reported symptoms in mTBI that impact on the interpretation. Indeed, some individuals may hold misconceptions of their abilities prior to their mTBI, leading to exaggerated symptom reporting [12,51], and others may not accurately report their symptoms to clinicians, as they feel pressure to down-play their symptoms [12,51].

Ultimately, reliance on self-reported symptoms alone for diagnosis and monitoring of mTBI recovery may miss underlying physiological issues that could become persistent clinical conditions. Objective measures may provide a more accurate reflection of physiological performance (i.e., the task being performed) and could provide informative data that compliments traditional VOMS self-report symptoms (i.e., the perception of symptoms during the task). The iVOMS is unique in that the objective (iVOMS) and subjective (VOMS) assessment is performed simultaneously, which may provide novel insights into symptom and physiological recovery within a single clinical assessment (i.e., reducing patient and test burden).

4.3. Study limitations

There are several limitations in the current study. This study was an add-on to a larger clinical trial in mTBI [19], and therefore did not have a formal sample size calculation, regardless this is one of the largest studies of eye-tracking in an mTBI cohort [16]. Within the protocol, we did not conduct a comprehensive ophthalmological or cognitive assessment of the groups, which would provide further insights into the multifaceted symptomology and iVOMS performance [16,52]. Another limitation was baseline demographic differences in our control cohort, a sample of convenience. To mitigate this limitation, we controlled for these differences in our statistical analysis, as they have been found to influence mTBI severity and eye-tracking results [53–56]. Furthermore, there may be other confounders that we did not consider (e.g., ophthalmic, vestibular or cognitive function, motion sickness, etc.). Additionally, due to the age range used (18+ years old) the findings cannot be generalised to paediatric patients. It was beyond the scope of this initial validation study to perform extensive analysis on the iVOMS outcomes to determine their sensitivity to differentiate mTBI from controls compared to the VOMS subjective symptom scores, or to determine the most sensitive iVOMS outcome measure for differentiating groups (e.g., through Receiver operator curves or logistic regression). However now that this initial validation study has shown analytical validation of eye-tracking outcomes and some significantly different between group iVOMS outcomes, future studies could further investigate these aspects. Another limitation in our analysis is that we did not control for multiple comparisons. However, considering the exploratory nature of this study, we chose to rather restrict the alpha value in order to avoid discounting actual findings due to sample size or number of comparisons being made [57–59]. Future studies that are specifically powered for multiple comparisons could apply such methods. Finally, the study setting was in a laboratory, rather than a clinic, the testing could easily be performed in any environment, and this could be explored in future work.

5. Conclusions

This is the first study to use a mobile eye-tracker to instrument the VOMS and validate algorithmic assessment of eye movement detection during each of the tests in both mTBI and healthy individuals. The findings showed that the iVOMS was able to find significant differences between healthy controls and those with mTBI in some key measurements, but outcomes did not relate to self-reported symptom scores. The iVOMS provided insight into eye movement features that were not observed in the clinical VOMS, and therefore, it may provide additional data to assist with diagnosis or injury recovery tracking. Future research is needed to test the sensitivity and robustness of the iVOMS outcome measures across different mTBI cohorts or response to interventions, which is a necessary precursor to establishing a clinically meaningful change or threshold.

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Ethical approval

Work on human beings that is submitted to *Medical Engineering & Physics* should comply with the principles laid down in the Declaration of Helsinki; Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989. You should include information as to whether the work has been approved by the appropriate ethical committees related to the institution(s) in which it was performed and that subjects gave informed consent to the work.

CRediT authorship contribution statement

Lisa Graham: Project administration, Resources, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Dylan Powell:** Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Kody R. Campbell:** Data curation, Project administration, Resources, Writing – original draft, Writing – review & editing. **Rosie Morris:** Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Rodrigo Vitorio:** Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Lucy Parrington:** Data curation, Project administration, Resources, Writing – original draft, Writing – review & editing. **Prokopios Antonellis:** Data curation, Project administration, Resources, Writing – original draft, Writing – review & editing. **Alan Godfrey:** Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Laurie A. King:** Conceptualization,

Data curation, Funding acquisition, Project administration, Resources, Writing – original draft, Writing – review & editing. **Samuel Stuart:** Conceptualization, Funding acquisition, Project administration, Resources, Formal analysis, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors confirm there are no competing interests. All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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