

Oculomotor, Vestibular, and Reaction Time Effects of Sports-Related Concussion: Video-Oculography in Assessing Sports-Related Concussion

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Objective: The purpose of the study was to test the ability of oculomotor, vestibular, and reaction time (OVRT) metrics to serve as a concussion assessment or diagnostic tool for general clinical use. **Setting and Participants:** Patients with concussion were high school-aged athletes clinically diagnosed in a hospital setting with a sports-related concussion ($n = 50$). Control subjects were previously recruited male and female high school student athletes from 3 local high schools ($n = 170$). **Design:** Video-oculography was used to acquire eye movement metrics during OVRT tasks, combined with other measures. Measures were compared between groups, and a subset was incorporated into linear regression models that could serve as indicators of concussion. **Measures:** The OVRT test battery included multiple metrics of saccades, smooth pursuit tracking, nystagmoid movements, vestibular function, and reaction time latencies. **Results:** Some OVRT metrics were significantly different between groups. Linear regression models distinguished control subjects from concussion subjects with high accuracy. Metrics included changes in smooth pursuit tracking, increased reaction time and reduced saccade velocity in a complex motor task, and decreased optokinetic nystagmus (OKN) gain. In addition, optokinetic gain was reduced and more variable in subjects assessed 22 or more days after injury. **Conclusion:** These results indicate that OVRT tests can be used as a reliable adjunctive tool in the assessment of concussion and that OKN results appear to be associated with a prolonged expression of concussion symptoms. **Key words:** concussion, oculomotor, optokinetic, OVRT, reaction time, smooth pursuit, vestibular, video-oculography

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ACCURATE DIAGNOSIS and optimal treatment of concussive injuries are hindered by the lack of a truly objective test for the diagnosis of concussion.¹ Although current diagnostic tools, such as neuropsychological/neurocognitive testing, and brain imaging (eg, CT, MRI, and fMRI), are important concussion assessment tools, these techniques address only some of the neurofunctional or neuroanatomical domains potentially impacted by concussion.^{2–8} An innovative adjunct to current concussion assessment practice is to use high spatial and temporal resolution measurements

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of eye movement reflexes and responses to specific stimuli or tasks, generally known as video-oculography. Aberrations in eye movements in saccades, smooth pursuit, nystagmus, and vergence have proven to be informative indicators of brain injury,⁹⁻²⁵ as have measurements of vestibular functions,^{10,11,18,19,26} and reaction time performance.²⁷⁻³⁰

In this study, we used a video nystagmography (VNG) device to assess oculomotor, vestibular, and reaction time (OVRT) function in a population of high school athletes who had sustained head injuries, and for whom a concussion was diagnosed clinically. We tested the specific hypothesis that these OVRT measures can reliably distinguish concussed subjects from similarly aged controls, and thereby serve as a sensitive concussion assessment tool. We performed tests over a broad range of post-event times, from 1 to 328 days. For comparison, we assessed normal function in high school athletes with no history of concussion. Multiple deficits were found in the concussion relative to the control population. Our results suggest that a diverse repertoire of OVRT tests can be used to construct a diagnostically valuable classification procedure generated from measures of the neurophysiological consequences of concussion. Our results also suggest that at least one metric, optokinetic nystagmus (OKN) gain, remains impaired for a longer period than other OVRT metrics.

MATERIALS AND METHODS

All procedures were approved by the Allegheny General Hospital Institutional Review Board and were in compliance with the National Institutes of Health's guidelines conducting research with human subjects.

Subject populations

Concussed subjects were high school-aged athletes clinically diagnosed with a sports-related concussion. Concussion was defined as a transient alteration of normal brain function typically affecting orientation and memory due to an external mechanical force, which may have involved loss of consciousness; concussion was considered equivalent to mild traumatic brain injury (mTBI). No subject met criteria for moderate or severe TBI. The athletes were referred to the Allegheny General Hospital Concussion Center because of ongoing symptoms and/or signs of a concussion, with no specific criteria for patient referral. Only those patients for whom the diagnosis of concussion was confirmed by the director of the Sports Medicine Concussion Clinic or by 1 of 2 neurology attendings in the Neurology Concussion Clinic were recruited and enrolled consecutively in the study. Inclusion criteria were male and female patients 13 to 18 years of age who were able and willing to assent or consent; a parent or legal guardian provided consent for

those patients under 18 years of age. Exclusion criteria were brain injury resulting from a penetrating wound to the head, neck, face, or brain, history of schizophrenia or major depression, and previous concussion with incomplete symptom recovery.

Fifty concussed subjects (26 male, 24 female, mean age 15.2 years) were enrolled (see Table 1). Postinjury times ranged from 1 to 328 days (mean 22.1, median 9). Subjects performed a series of OVRT tests, as described later (*testing protocol*, Table 2).

Control subjects were male and female athletes recruited from 3 local high schools before the start of their athletic season. Control subjects were removed from analysis when there were (1) a history of concussion; (2) indeterminate data regarding a possible previous concussion; and (3) poor data quality, missing data, or other technical problems with subject data or records.

One hundred seventy control subjects (range 11-18, mean age 15.5 years) were analyzed; note is made that there was only 1 subject aged 11 years; the next lowest age of a subject was 13 years. We had incomplete sex information for the control population; therefore, an exact distribution of this demographic detail could not be calculated. However, based on the number of available sex-identified control subjects, we estimated that the male-female ratio in the control group was roughly 2:1.

Testing protocol

Assessments were performed on a combined eye-tracking, stimulation, and analysis system (I-Portal VNG). Video data from both eyes were recorded at 100 Hz and synchronized with stimulus presentation. Tests were conducted in dim light with the subject seated in front of a wide white reflective screen or other featureless surface. Full-field OKN stimuli were created by a rotating projector. Other visual stimuli were projected by a 650-nm laser onto the display/testing surface. Auditory stimuli were presented using a 5-V piezoelectric buzzer. All stimulus ranges given later had an estimated variance of 10% during this study.

Smooth pursuit

Subjects performed 6 smooth pursuit (SP) tasks, 3 horizontal and 3 vertical. Subjects tracked a laser-projected target that travelled with a sinusoidal velocity profile across -10° to 10° of visual angles at 3 frequency profiles: 0.1, 0.75, and 1.25 Hz for horizontal, and 0.1, 0.5, and 0.75 Hz for vertical (see Table 2 for details). Assessed measures included position and velocity gain, velocity gain asymmetry, the presence of saccadic movement, and the latency to initiate SP tracking.

Saccades

For saccade testing, targets were displayed consecutively at pseudorandom locations along horizontal or

TABLE 1 *Demographic and injury information for the concussion subjects*

Age, y	Sex	Days between injury and initial visit	Sports	Impact site	Injury description	Postconcussion symptom severity score
17	Male	13	Football	Occipital	Back of head hit ground and bounced after being tackled	61
14	Male	17	Football	Unknown	Helmet-to-helmet impact	14
16	Female	19	Cheerleading	Frontal	Struck in the forehead by a peer	34
13	Female	37	Cheerleading	Occipital	Struck in back of head by a peer's feet	58
16	Male	9	Soccer	Temporal (left)	Soccer ball struck left temporal area	38
15	Female	19	Softball	Frontal (left)	Hit in forehead by softball pitch during warm-up	41
15	Female	1	Ice hockey	Temporal (left)	Hockey puck struck left temporal area of helmet	7
15	Male	7	Skiing	Occipital	Fell backward and struck back of head	23
18	Female	12	Volleyball	Occipital	Fell backward and hit back of head on gym floor	36
17	Male	53	Hockey	Chin	Struck by another player under chin during game	0
14	Male	8	Football	Temporal (left)	Helmet-to-helmet impact	46
17	Male	13	Soccer	Right side of head	Struck by another player during game	22
14	Female	4	Cheerleading	Right side of head	Struck by another cheerleader's shoulder/upper back	22
14	Male	7	Football	Frontal	Accelerating helmet-to-helmet collision	20
16	Male	9	Football	Frontal	Helmet-to-helmet impact	No data
14	Female	4	Cheerleading	Occipital	Fell approximately 8 ft, landed on floor mat and hit head	11
14	Male	8	Football	Occipital	Fell backward over another player, striking back of head	30
15	Male	5	Football	Temporal (right)	Hit on right side of head (helmet-to-helmet impact)	1
16	Female	4	Soccer	Temporal (left)	Struck by soccer ball on left side of head	51
14	Male	13	Football	Frontal	Helmet-to-helmet impact	1
16	Male	27	Football	Frontal	Helmet-to-helmet impact	7
14	Male	7	Hockey	Frontal	Fell and hit head off of boards surrounding rink	32
15	Male	64	Soccer	Posterior neck (left)	Struck from behind in left posterior neck area	7
14	Male	4	Lacrosse	Maxilla (right)	Hit on right side of face with lacrosse stick	15
17	Female	39	Cheerleading	Occipital (left)	Kicked in left occipital area of head	30
16	Male	4	Hockey	Temporal (left)	Elbow to left temporal area (wearing helmet) and fell to ice (amnesic)	28

(continues)

TABLE 1 Demographic and injury information for the concussion subjects (Continued)

Age, y	Sex	Days between injury and initial visit	Sports	Impact site	Injury description	Postconcussion symptom severity score
17	Female	27	Softball	Posterior inferior skull	Struck back of head with bat at the end of swinging motion	4
17	Female	7	Cheerleading	Frontal (right)	Struck by another cheerleader in forehead (right)	59
13	Female	11	Cheerleading	Occipital (left)	Fell during cheerleading stunt and hit occipital (left) area on floor	41
17	Female	97	Hockey	Occipital	Head-on collision with player, then fell backward, striking back of head	18
14	Female	9	Ice Skating	Occipital	Fell backward and struck back of head (loss of consciousness)	34
17	Male	328	Hockey	Frontal	Struck by another player and fell, hitting front of head on ice	72
13	Female	8	Basketball	Frontal (right temple)	Hit by another player (no specific details provided)	12
13	Male	5	Football	Occipital	Hit in back of head while being tackled	16
15	Female	21	Basketball	Unknown	Hit in head with basketball	68
15	Female	14	Cheerleading	Top of head	Struck in the top of head by peer's forearm	23
16	Male	9	Wrestling	Frontal (temple)	Struck by another wrestler's head during practice	44
16	Female	6	Basketball	Frontal	Hit front of head on wall diving for a loose ball	28
15	Female	8	Cheerleading	Top of head	Struck by a peer on the crown of head	60
17	Female	11	Basketball	Occipital	Fell backward and hit head after being charged	1
13	Male	43	Wrestling	Frontal/temporal (right)	Hit front of head while wrestling	16
14	Female	15	Cheerleading	Occipitoparietal (right)	Cheerleader landed on right occipitoparietal portion of head	10
16	Male	15	Soccer	Temporal (left)	Forearm blow to left temporal region of head (right side hit ground)	4
17	Female	12	Basketball	Frontal (left)	Hit in head with basketball	46
14	Female	6	Soccer	Right side of head	Soccer ball struck right side of head	62
13	Male	3	Football	Frontal	Helmet-to-helmet impact	33
14	Female	4	Soccer	Frontal	No description provided	9
15	Male	6	Gym class	Unknown	Hit head on turf while attempting to complete a tackle	17
15	Male	30	Soccer	Temporal/parietal (right)	Soccer ball struck head	34
18	Male	5	Football	Unknown	Hit in head by opponent and subsequently hit head on ground	10

TABLE 2 *Test battery protocol used to assess oculomotor, vestibular, and reaction time function*

Test	Study protocol	Example measures
Spontaneous nystagmus	1 cycle—stimulus light is projected at a central fixation point for 5.65 s, followed by light off for 10 s	Peak slow-phase nystagmus velocity with target off (vertical and horizontal)
Optokinetic nystagmus	2 segments—Full-field random-dot stimulus continually moves one direction horizontally for 10 s, and then in the opposite direction for 10 s, at an estimated 23.4°/s (low-speed OKN test) or 70.3°/s (high-speed OKN test) velocity	Gain of slow-phase nystagmus and gain asymmetry, area under fast-phase fit
Smooth pursuit—horizontal	Single light stimulus moves smoothly right, then left, with sinusoidal velocity and maximum displacement of 10°; 3 cycles at 0.1 Hz, 6 cycles at 0.75 Hz, and 6 cycles at 1.25 Hz	Gain of eye position and velocity relative to stimulus, velocity gain asymmetry, presence of saccadic movement, initiation latency
Smooth pursuit—vertical	Same as horizontal, but with 3 cycles at 0.1 Hz, 4 cycles at 0.5 Hz, and 6 cycles at 0.75 Hz	Same
Saccade—random horizontal	29 cycles—single light stimulus projected at random horizontal displacements and time, with maximum displacement of 30°, and time between stimuli 1.1-2.0 s.	Saccade onset latency, accuracy, velocity, area under main-sequence fit
Saccade—random vertical	Same as horizontal, but all targets appeared on the central vertical axis	Same
Saccade—predictive horizontal	20 cycles—similar to horizontal saccade, but with a predictable series embedded after a series of random saccades: single light stimulus is projected at 10° left or right displacement (alternating) with a fixed 0.65-s interval	Ability to adapt to predictable timing (first predicted, amount and percent predicted)
Saccade—antisaccade horizontal	16 cycles projected at random horizontal displacements and time, with maximum displacement of 20°, and time between stimuli 2-2.85 s. Subject is instructed to look away from the target, and target returned to center after each target presentation	Saccade latency, accuracy, velocity, percentage of incorrect prosaccades
Saccade and reaction time	29 cycles—single light stimulus projected at random horizontal displacements and time, with maximum displacement of 30°, and time between stimuli 1.5-2.5 s. Subject asked to look to target and click left or right buttons depending on relative direction of target movement	Saccade onset latency, accuracy, velocity; button press latency
Visual reaction time	9 trials—random single light stimulus appears at center of vision and subject using his/her dominate hand clicks on button as quickly as possible	Mean latency and latency standard deviation across trials for subject
Auditory reaction time	11 trials—random auditory stimulus 85 dB presented and subject using his/her dominate hand clicks on button as quickly as possible	Mean latency and latency standard deviation across trials for subject
Subjective visual—vertical	Up to 4 trials—straight line stimulus appears tilted off vertical axis, 10° and 15° displacement clockwise and counterclockwise. Subject asked to press buttons to tilt line back to vertical alignment	Mean angular error from vertical axis and standard deviation across trials for subject
Subjective visual—horizontal	Up to 4 trials—straight line stimulus appears tilted off horizontal axis, 12° and 15° displacement clockwise and counterclockwise. Subject asked to press buttons to tilt line back to horizontal alignment.	Mean angular error from horizontal axis and standard deviation across trials for subject

Abbreviation: OKN, optokinetic nystagmus.

vertical axes. We evaluated latency to initiate a saccade, accuracy, and peak velocity relative to a normative threshold and as a function of saccade amplitude (saccadic “main sequence”).³¹ Subjects also performed predictive saccade tests (timing designed to evaluate prediction of target movement) and antisaccade tests (subjects instructed to consciously look in the opposite direction of the target).

Analysis of saccade results revealed that, for technical reasons, the individual stimulus presentation times were more variable with an estimated mean of 80-ms longer duration (per stimulus) for control subject test sessions than sessions for concussed subjects (for all saccade test types, including the saccades and reaction time test, below). This anomaly may have affected saccade final accuracy measurements (accuracy after all corrective saccades) and predictability of saccades in the predictive saccades test. Despite this technical discrepancy, we retained saccade metrics in our results since the only measures we report here as significant are low saccadic velocities on the saccades and reaction time tests, a measure not impacted by the discrepancy.

Optokinetic nystagmus

The OKN response was tested using a horizontally moving field of illuminated dots created by a rotating projector at an estimated 23.4° or 70.3°/s (separate tests) that subjects viewed passively. Stimuli moved in one direction for 10 seconds, paused briefly, and then reversed for 10 seconds (initial direction was not the same for all subjects). We measured velocity gain during the slow nystagmus phases (ie, the ratio of eye vs stimulus velocity), as the eyes tracked the stimulus. We computed asymmetry between the leftward and rightward directions as follows:

Asymmetry = Absolute value

$$[100\% \times (\text{Gain}_{\text{dir1}} - \text{Gain}_{\text{dir2}})/(\text{Gain}_{\text{dir1}} + \text{Gain}_{\text{dir2}})],$$

where $\text{Gain}_{\text{dir1}}$ and $\text{Gain}_{\text{dir2}}$ are the gain values computed separately for the 2 stimulus directions. We also assessed the OKN fast phases by constructing a main sequence plot (velocity vs amplitude) similar to that used for saccade analysis.³¹ Our metric of fast-phase performance is the integrated area under an exponential fit performed on the main sequence graph (maximum of positive vs negative areas).

Vestibular tests

We included 3 vestibular function tests. For subjective visual vertical and horizontal (SVV and SVH) tests, subjects used left and right buttons to rotate a laser-drawn line until it was either vertical or horizontal. For spontaneous nystagmus (SN), a fixation target was presented

for 5.65 seconds, followed by a period of 10 seconds with no fixation target.

Reaction time

We assessed reaction time (RT) responses using button presses in response to visual and auditory stimuli (separate tests). To reduce the effects of erroneous button presses during the RT tests, the first valid response time and all values outside the range of 80 to 1500 ms were removed from the RTs. Then all outliers outside 3 standard deviations from the mean of the remaining points for each subject were removed. The retained points were used in the calculation of mean RT and its standard deviation.

In the saccade and RT test (SRT), we combined a standard prosaccade task with the visual RT test to assess oculomotor, cognitive, and manual interactions (see Table 2 for details). Subjects were instructed to look toward the lighted target when it moved, and press either the left or right button depending on whether the target moved to the left or right relative to its last position. The automatic removal of RT values performed for the other RT tests was not performed for the SRT test.

Data analysis

Performance measures were computed using the assessment system software (I-Portal and VEST, Neuro Kinetics Inc, Pittsburgh, Pennsylvania). Data were calibrated for position by the comparison of eye movement to fixation positions with known displacement, and refined as needed by position comparison in the slowest SP tests. Acquired data for the OVRT tests were then manually analyzed in the VEST software by a data analyst blinded to the concussion status of each subject (control vs concussion group). Data were filtered or partially removed on a test-by-test basis by manual adjustment of VEST software controls according to standard operating guidelines/procedures for the removal of artifacts (eg, blinks, recording noise, temporary failures of eye tracking, shifting of goggles, erroneous responses, or ones not related to the task) to separate eye movement signals from other recording noise, and to segregate saccadic activity from pursuit activity. Individual tests for some subjects were removed from analysis when the data quality was judged (not blinded to concussion diagnosis in all instances) to be inadequate for accurate measurement or produced analytic errors.

Subsequent population analyses were performed on the acquired measures using SPSS (IBM, Armonk, New York), Excel (Microsoft, Redmond, Washington), and custom software written in LabVIEW (National Instruments, Austin, Texas). All significance values reported for comparison of control versus concussed subjects were by the Mann-Whitney *U* test, although we

report the distributions using customary parametric statistics (mean \pm standard deviation), even though some of our variables did not adhere to a normal distribution. A subset of all measures produced by the software was assessed (to reduce the number of variables compared) resulting in 87 variables. To avoid type I statistical errors, we chose a highly conservative α value of .000575 (.05/87 variables) when determining comparison significance. To assess whether significantly different metrics were different at later time points following injury, we compared 16 variables (Mann-Whitney U) for the subset of concussed patients tested 22 or more days after injury ($n = 10$) versus the control group, using an α value of .00313 (.05/16 variables).

We constructed standard regression models using measures from the test batteries, with concussion/nonconcussion group membership as the dependent variable. The first regression model was a "Forward: conditional" logistic model (SPSS Statistics, version 23), used to identify a small viable subset of variables, which produced good classification results (entry and removal values for variable score statistics were 0.005 and 0.01, respectively). The procedure initially identified 5 variables; however, 2 of these (horizontal saccade final accuracy and antisaccades undershoot) were removed from consideration in model building because of the confound created by different saccade test stimulus durations (see the Saccades subsection, earlier). The variables identified by this method were then reassessed and subjected to cross-validation using custom-built software written in LabVIEW. This custom software

constructed linear regression models from the identified variable set using the LabVIEW "Solve Linear Equations" function (which finds the solution matrix X for $AX = Y$ matrix equations). Standard cross-validation was performed by leaving a random subset of cases out of model generation (5 from both the concussion and control groups), and computing the model classification success on the subset left out. This "leave-out" validation was repeated 500 times, and the mean and standard deviation of classification accuracies are reported. Results fields from individual tests were imputed (for regression, but not Mann-Whitney U comparison) if the test was missing from the data (eg, the test was not acquired), or if the fields were removed from analysis because the test could not be reliably analyzed. Imputation for each field was performed by standard "Hot Deck" imputation, meaning that replacement values were randomly drawn from the field's values among other subjects in the same group (control group or concussion group). Cutoff thresholds other than 0.5 (eg, Table 3) were chosen manually, but selected to reflect where models achieved a nearly even ratio between sensitivity and specificity.

RESULTS

We compared the results of 87 OVRT test metrics between 170 controls and 50 concussed subjects. Metrics that were significantly different are presented first. Following these results are the classification models (concussion vs control) developed using logistic and

TABLE 3 Concussion classification success rates of a forward conditional logistic regression model (first column, top left) and a linear regression model (second column, top right)

Forward conditional logistic regression		Linear regression model	
0.5 cutoff, all data		0.5 cutoff, all data	
Sensitivity	76.0%	Sensitivity	68.0%
Specificity	95.9%	Specificity	96.5%
Correctly classified	91.4%	Correctly classified	90.0%
0.28 cutoff, all data		0.365 cutoff, all data	
Sensitivity	90.0%	Sensitivity	92.0%
Specificity	88.8%	Specificity	89.4%
Correctly classified	89.1%	Correctly classified	90.0%
Cross-validation linear models ($n = 500$)			
Sensitivity	86.8% (15.1%)		
Specificity	89.9% (13.4%)		
Correctly classified	88.3% (9.7%)		

Each model was tested on all data used in the study, and the linear model used only variables isolated by the logistic model process. The combined results of 500 cross-validations are shown (first column, bottom left), where for each run 5 cases were set aside from each of the 2 groups.

standard linear regression techniques. After identifying 16 significant concussion-related metrics, we also evaluated these metrics for the subset of 10 subjects evaluated 22 or more days after injury.

Smooth pursuit tracking

In our study population, initiation latency (see Figure 1) was significantly different for horizontal SP tests performed at 0.75 Hz (concussion 253 ± 106 ms; control 214 ± 59 ms; $P < .000575$) and at 1.25 Hz (concussion 243 ± 59 ms; control 225 ± 98 ms; $P < .000575$), and for vertical SP tests performed at 0.5 Hz (concussion 238 ± 49 ms; control 213 ± 65 ms; $P < .000575$) and 0.75 Hz (concussion 225 ± 58 ms; control 207 ± 75 ms; $P < .000575$). At 1.25 Hz (horizontal), concussion subjects also demonstrated a significantly reduced position gain (eye position/stimulus position) relative to control subjects (concussion 0.72 ± 0.18 ; control 0.82 ± 0.17 ; $P < .000575$), and reduced velocity gain (concussion 0.67 ± 0.18 ; control 0.77 ± 0.17 ; $P < .000575$).

Saccades

Significant differences were not seen for saccades during the random horizontal, vertical, and antisaccades tests, or during the predictive saccade test. In addition, no significant difference was seen for prosaccade errors on the antisaccades test.

In the combined SRT test, in which subjects were required to respond with both saccadic movement and button presses, we found that the percentage of saccade velocities that fell below a normative velocity threshold was significantly higher for the concussion group than for controls (concussion $7.2\% \pm 11.5\%$; control $1.8\% \pm 4.7\%$; $P < .000575$; Figure 2).

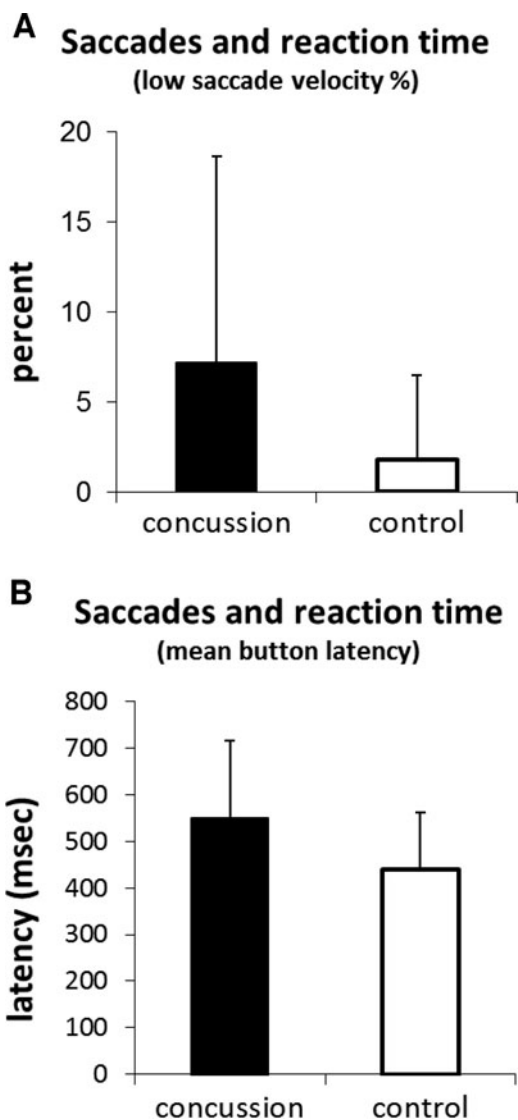


Figure 2. Results for the SRT test. (A) Concussion subjects demonstrated reduced saccade velocity during the combined test, as measured by the percentage of saccades to horizontal targets that fell below a threshold velocity (where the threshold varied by amplitude, see Methods; $n = 146$ controls, 43 concussion subjects). (B) Concussion subjects also had increased latencies to press a left or right button indicating direction of saccade target shift ($n = 146$ controls, 43 concussion subjects). SRT indicates saccade and reaction time.

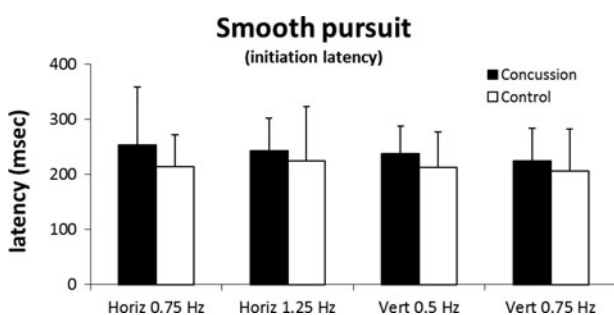


Figure 1. Horizontal and vertical SP test initiation latencies. Shown are the means \pm SD for the latencies to start SP tracking at the start of SP tests. Values are shown for concussion subjects (black bars, $n = 50, 49, 49,$ and 48 , from left to right) and controls (white bars, $n = 170, 169, 165,$ and 165 , from left to right). Differences are small but significant (by Mann-Whitney U) in the 4 SP tests shown. SP indicates smooth pursuit; SD, standard deviation.

Optokinetic nystagmus

Horizontal OKN response was tested at 2 velocities: 23.4° (low speed) and 70.3° (high speed; Figure 3A) of visual angle/second, and we measured the slow-phase nystagmus velocity gain. This gain measure was computed as a mean of the velocity of all nystagmus beats for a subject relative to stimulus velocity (see Figure 3B), and was significantly reduced for the concussion group during the low-speed OKN test (concussion 0.78 ± 0.17 ; control 0.95 ± 0.09 ; $P < .000575$), and the high-speed

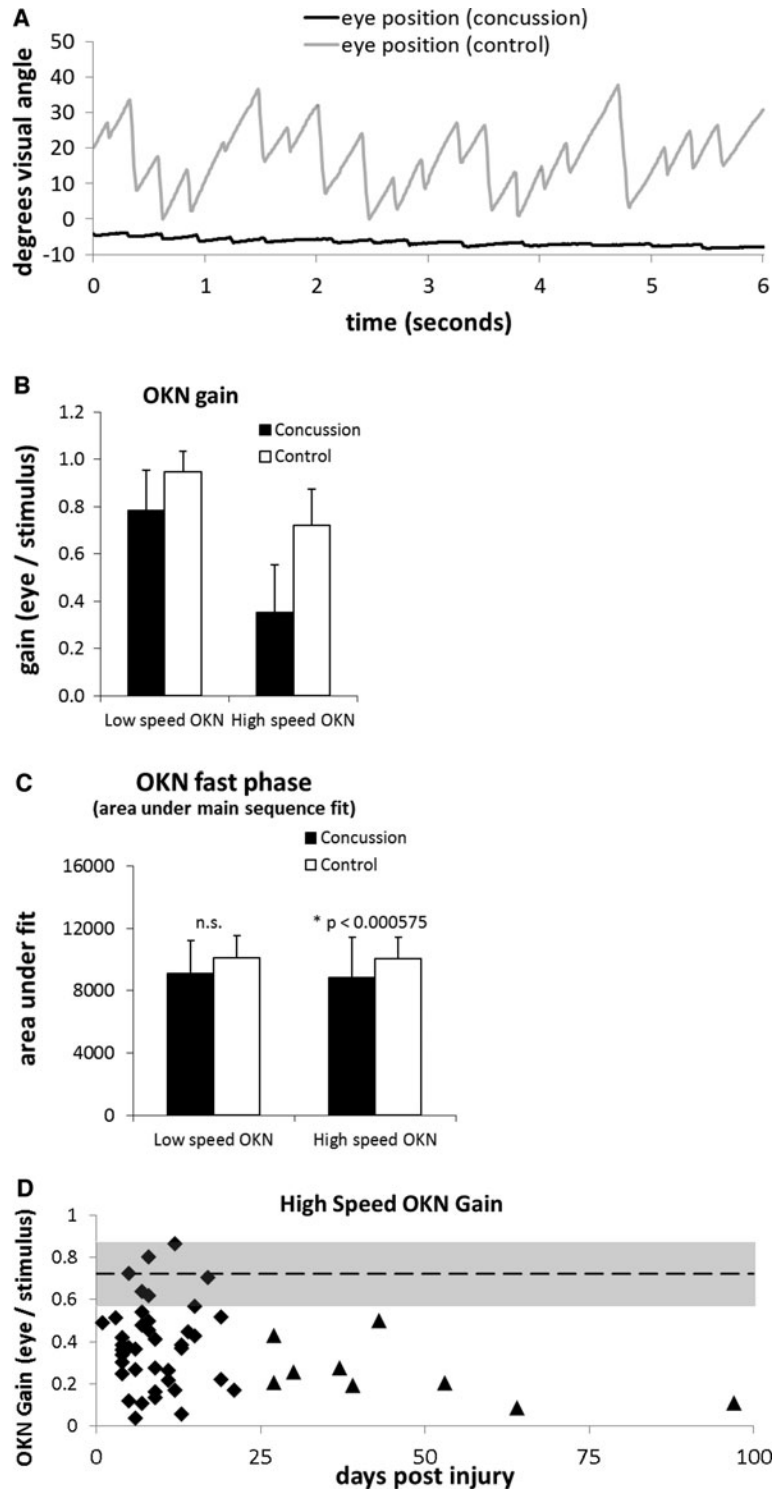


Figure 3. OKN test results. (A) Exemplary eye position traces during the high-speed OKN test show a notably impaired or suppressed OKN reflex for a concussed subject (black line) as compared with a control subject (gray line). (B) Comparison of OKN gain (ratio of eye velocity to stimulus velocity) results between concussion ($n = 50$, black bars) and control ($n = 166$, white bars) groups. (C) Comparison of OKN “area under the main sequence fit” results for concussion subjects ($n = 50$ black bars) showing reduced fast-phase velocity compared with controls ($n = 166$, white bars) only for the high-speed OKN test. (D) High-speed OKN gain was significantly lower for patients with concussion tested 22 or more days postinjury ($n = 10$, black triangles, one subject at 328 days not plotted, gain = 0.06). Control mean (black dashed line) and 1 SD (gray box) are shown for comparison (0.72 ± 0.15). OKN indicates optokinetic nystagmus; SD, standard deviation.

OKN test (concussion 0.35 ± 0.20 ; control 0.72 ± 0.15 ; $P < .000575$). Concussion subjects had significantly more gain asymmetry (unequal velocity gain in the leftward and rightward nystagmus directions) during the high-speed OKN test (concussion 21.2 ± 18.9 ; control 8.6 ± 9.8 ; $P < .000575$), and a higher variability in velocity gains as measured by the gain standard deviation across all nystagmus beats for each subject (low speed, concussion 3.9 ± 1.9 ; control 2.8 ± 1.6 ; $P < .000575$; high speed, concussion 13.6 ± 4.5 ; control 11.2 ± 4.1 ; $P < .000575$).

We also evaluated the fast phases of OKN nystagmus beats at the 2 speeds, and quantified fast-phase velocity performance as an area under a main sequence curve fit (see Methods; Figure 3C). This fast-phase area value was significantly reduced in concussion subjects for the high-speed OKN test (concussion 8868 ± 2541 ; control 10035 ± 1383 ; $P < .000575$), suggesting a reduction in the velocity/distance ratio of fast-phase nystagmus beats in patients with concussion.

In addition, we evaluated the 16 metrics that were significantly different between the concussed and control

groups for the subgroup of 10 patients with concussion recorded at 22 days or more postinjury. OKN gain metrics were the only metrics significantly different in this postconcussive group, namely low speed gain (22 plus-day concussion gain 0.77 ± 0.16 ; control 0.95 ± 0.09 ; $P < .00313$), and high speed gain (22 plus-day concussion gain 0.23 ± 0.14 ; control 0.72 ± 0.15 ; $P < .00313$; Table 4 and Figure 3D), as well as high-speed gain standard deviation (22 plus-day concussion 14.7 ± 2.6 , control 11.2 ± 4.1 , $P < .00313$).

Reaction time

Manual RT was not significantly different for the standard visual RT or auditory RT tests. In the more complex SRT test, however, a significant increase in left, right, and mean button press latency was observed for the concussion group (mean latency, concussion 550 ± 167 ms; control 440 ± 122 ms; $P < .000575$).

Vestibular tests

No significant differences were seen for measures in the SVH, SVV, or SN tests.

TABLE 4 Variables identified as significantly different for all concussed subjects at all time points (first column)

Significant OVRT variables, all subjects/all time points (P value $< .000575$, concussion vs control groups)	P value per variable, ≥ 22 d, concussion vs control ($n = 10$; $\alpha = .00313$)
Low-speed OKN gain (grand mean of leftward and rightward segment means)	.00011
Low-speed OKN gain variability (maximum standard deviation from leftward and rightward segments)	.016
High-speed OKN gain (grand mean of leftward and rightward segment means)	.00000033
High-speed OKN gain asymmetry (asymmetry of mean gains of leftward and rightward segments)	.0032
High-speed OKN gain variability (maximum standard deviation from leftward and rightward segments)	.0031
High-speed OKN area under fast-phase fit (maximum of negative and positive velocity beat fits)	.48
SRT button latency, mean (grand mean of left and right)	.46
left button latency (mean of left button RTs)	.51
right button latency (mean of right button RTs)	.49
SRT low velocity % (maximum of each eye and direction)	.0045
SP horizontal 1.25-Hz velocity gain (mean of leftward and rightward movement)	.38
SP horizontal 1.25-Hz position gain	.22
SP horizontal 0.75-Hz pursuit initiation latency	.14
SP horizontal 1.25-Hz pursuit initiation latency	.046
SP vertical 0.5-Hz pursuit initiation latency	.16
SP vertical 0.75-Hz pursuit initiation latency	.086

Abbreviations: OKN, optokinetic nystagmus; OVRT, oculomotor, vestibular, and reaction time; SP, smooth pursuit; RT, reaction time; SRT, saccade and reaction time.

For each variable, we compared the results for concussed subjects tested at 22 or more days after injury (second column) to the full control population. Of these, only OKN gain on the low- and high-speed OKN tests, and high-speed gain variability (*italicized*) were significantly different between the 22 or more days' concussion subjects and the control group ($P < .00313$).

Separation of groups

Because of the many significantly altered OVRT metrics between concussion and control groups, we hypothesized that a combination of multiple metrics could create a strong clinical indicator of concussion condition. To test this hypothesis, we constructed a logistic regression classification model using our measurements as inputs, and membership in the concussion group as outputs.

At a default cutoff threshold of 0.5, the model correctly classified 91.4% of the subjects in the model training set. The model had a specificity of 95.9% (163 out of 170 controls classified correctly) but a sensitivity of only 76.0% (38 out of 50 concussion subjects). At a more optimized threshold of 0.28, the model correctly classified 89.1% of subjects, with a specificity of 88.8% and a sensitivity of 90.0% (see Table 3). As a measure of classification accuracy across thresholds, we generated a standard receiver-operating characteristic curve (see Figure 4) and measured an area under the curve of 0.96.

Forward conditional regression adds variables in steps, and in our model the regression terminated after 3 steps, choosing 3 significant variables: high-speed OKN gain,

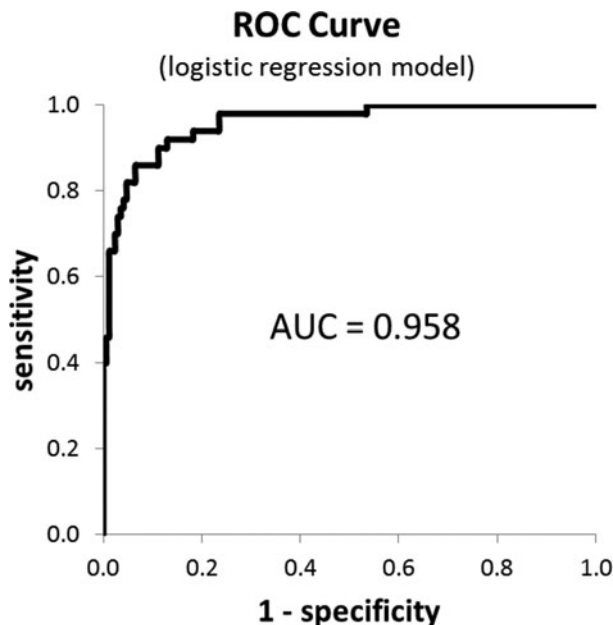


Figure 4. ROC curve for the first logistic regression model (forward conditional). The curve plots the sensitivity (true positives) versus the specificity (false positives, or 1-specificity) across a range of discrimination cutoff thresholds (0-1), of the model's ability to classify subjects as being in the concussion or control groups. The regression model included coefficients for 3 variables: high-speed OKN gain, SRT button latency, and SP initiation latency (0.5-Hz vertical test). OKN indicates optokinetic nystagmus; ROC, receiver-operating characteristics; SP, smooth pursuit; SRT, saccade and reaction time.

SRT button latency, and 0.5-Hz vertical SP initiation latency.

To test for overfitting, we constructed (nonlogistic) linear regression cross-validation models using these 3 variables, computing model coefficients using one set of subjects and tested on another (see Methods for details). The mean success rates over all 500 cross-validation models (cutoff threshold of 0.365, see Table 3) remained robust (sensitivity $86.8\% \pm 15.1\%$; specificity $89.9\% \pm 13.4\%$; overall $88.3\% \pm 9.7\%$).

DISCUSSION

A growing number of studies have investigated the effects of head injuries and concussions on oculomotor,^{9-25,32-37} vestibular,^{10,11,18,19,26} and reaction time²⁷⁻³⁰ (OVRT) performance. In this study we investigated whether combined OVRT measures can reliably distinguish concussed subjects from similarly aged controls in a population of high school students. The tests used in this study are fundamental assessments of vestibular and oculomotor function, many with a long history of use in the field of VNG.^{38,39} Also, the neural pathways controlling saccadic, SP, OKN, and other nystagmus movements have been extensively mapped and published, and, importantly, found to cover a broad range of neural territory,⁴⁰⁻⁴² making them ideal for assessments of general brain injury and/or dysfunction. We evaluated measurements independently by comparison of values between the 2 groups, and then collectively by constructing regression models.

Both approaches revealed metrics strongly related to the presence of a concussion, including alterations in SP tracking, delays in SP initiation, delayed RT and lower velocity on a combined saccade and button press task (SRT), and dramatically impaired optokinetic response during OKN tests. Importantly, OKN gains and gain variability were the only significant metrics observed in the subjects tested more than 3 weeks after injury ($n = 10$). This finding suggests that concussions can induce oculomotor deficits that extend beyond the first few weeks of recovery. Interestingly, the literature connecting objective optokinetic test results to concussions appears nonexistent, whereas symptoms induced by OKN testing have been reported.⁴³ It remains to be determined whether OKN can serve as a reliable indicator of long-term consequences of mTBI, and as a potential biomarker of protracted recovery.

Despite vestibular effects of concussion reported elsewhere,^{10,11,18,19,26} vestibular deficits were absent from our results. Importantly, the VNG device used in this study did not have the most robust tests of vestibular function, such as full body rotation tests. For the SVV, SVH, and SN tests, our lack of vestibular findings may also have resulted from performing tests in dim

light (not complete darkness), meaning that orienting or stabilizing cues may have been visible in the periphery for some subjects.

With this study we constructed multiple permutations of a regression model that reliably classified subjects as either control or concussed. Three variables were identified by this modeling: optokinetic gain (OKN test), RT latency in the SRT test, and initiation latency during SP. Given that there were 16 variables identified as significantly different between the 2 populations, it is worth noting that other combinations of OVRT metrics might create models with similar classification accuracy.

There were several limitations of this study. First, our demographic data regarding the sex of controls were inadvertently incomplete preventing a straightforward number and proportion of males and females, although from all available records the proportion was approximately 2:1. Test data quality was poor for many controls due to suboptimal testing techniques resulting in the removal of the controls from the subject group; testing imprecision and inaccuracy were minimized in the concussed subject group. Also, previous concussion history for control subjects was determined by self-report, and confirmation of concussion history by other means (eg, medical records) was not performed. Concussed subjects were assessed at a wide range of time points following their injury (ie, from 1 to 328 days; mean 22.1, median 9);

clearly a more restrictive time frame for evaluation would have enhanced the overall quality and interpretation of the test data, given that OVRT deficits appear to be variable, progressing and changing over time as underlying neurophysiological injury responses progress,¹⁹ resulting in a shifting (and not necessarily improving) profile of impairments. This possibility is supported by the observation that only 3 of the significant measures found for all subjects, OKN gain and gain variability metrics, were also significantly altered in the subgroup of concussed subjects who were recorded more than 3 weeks after injury, a finding that suggests the potential importance of OKN metrics in the longitudinal assessment of concussed patients during variable periods of recovery.

CONCLUSION

In summary, this study found that multiple OVRT metrics were strongly associated with the presence of a concussion both acute and chronic, suggesting their clinical utility in concussion assessment. These results indicate that concussions produce a broad range of motor and behavioral deficits that can be quantified objectively with high precision and accuracy using OVRT metrics. Given the feasibility of multivariate models as demonstrated in this study, combined with the potential for measurements to shift over the course of recovery, future studies employing a longitudinal series of assessments are warranted.

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