Laryngoscope Investigative Otolaryngology

The Use of Oculomotor, Vestibular, and Reaction Time Tests to Assess Mild Traumatic Brain Injury (mTBI) Over Time

Michael E. Hoffer, MD *; Carey Balaban, PhD*; Mikhaylo Szczupak, MD; James Buskirk, PT; Hillary Snapp, AuD; James Crawford, MD; Sean Wise, MD; Sara Murphy, MPH; Kathryn Marshall, PhD; Constanza Pelusso, MD; Sean Knowles; Alex Kiderman, PhD

Objectives: The objective of this work is to examine the outcomes of a set of objective measures for evaluating individuals with minor traumatic brain injury (mTBI) over the sub-acute time period. These methods involve tests of oculomotor, vestibular, and reaction time functions. This work expands upon published work examining these test results at the time of presentation.

Study Design: This study is a prospective age- and sex-matched controlled study.

Materials and Methods: The subject group was composed of 106 individuals with mTBI and 300 age- and sex-matched controls without a history of mTBI. All individuals agreeing to participate in the study underwent a battery of oculomotor, vestibular, and reaction time tests (OVRT). Those subjects with mTBI underwent these tests at presentation (within 6 days of injury) and 1 and 2weeks post injury. These outcomes were compared to each other over time as well as to results from the controls that underwent 1 test session.

Results: Six measures from 5 tests can classify the control and mTBI during Session 1 with a true positive rate (sensitivity) of 84.9% and true negative rate (specificity) of 97.0%. Patterns of abnormalities changed over time in the mTBI group and overall normalized in a subset of individuals at the third (final) testing session.

Conclusions: We describe an objective and effective second generation testing algorithm for diagnosing and following the prognosis of mTBI/concussion. This testing paradigm will allow investigators to institute better treatments and provide more accurate return to activity advice.

Key Words: mTBI, Concussion, Vestibular Disorders, Point of Injury Testing.

Level of Evidence: 3

INTRODUCTION

Mild traumatic brain injury (mTBI) is a public health concern that has become increasingly common.[1–10] This is true for both selected populations and in general from emergency department (ED) visits.[11–17] In addition, recognition of the injury pattern seems to be increasing in the general population. From the most recent available data, there has been an increase in the weighted rate of ED visits for TBI from 637 to 822 ED visits per every 100,000 visits.[12] Moreover, there has been an even steeper climb in visits for mTBI/concussion.[12] The increased prevalence of this disorder has resulted in a great deal of lay and scientific attention do this subject. However, despite the increased focus, very little progress has been made in a number of critical areas. In particular, accurate diagnostic and prognostic tests based on objective data have not been well studied or placed into widespread use. Current diagnostic techniques rely on self report or tests that require baseline data that is volitionally provided. As of yet no gold

This article was published online on April 12, 2017. After online publication, a footnote was added to indicate that the first and second author contributed equally to this work. This notice is included in the online version to indicate that both have corrected on April 18, 2017.

*Michael E. Hoffer, MD and Carey Balaban, PhD contributed equally to this work.

From the Department of Otolaryngology, (M.E.H., M.S., J.B., H.S., S.M., C.P., S.K.) and Department of Neurological Surgery (M.E.H.) Miller School of Medicine, University of Miami, Miami, Florida, U.S.A.; University of Miami Sports Performance and Wellness Institute (M.E.H., M.S., J.B., C.P.), Miami, Florida, U.S.A.; Department of Otolaryngology (C.B.), University of Pittsburgh, Pittsburgh, Pennsylvania, U.S.A.; Department of Otolaryngology (J.C., K.M.), Madigan Army Medical Center, Tacoma, Washington, U.S.A.; Naval Medical Center, San Diego (S.W., S.M.), San Diego, California, U.S.A.; and Neuro-Kinetics, Inc. (A.K.), Pittsburgh, Pennsylvania, U.S.A.

Editor's Note: This Manuscript was accepted for publication 16 February 2017.

Financial Disclosure and Conflict of Interest: Alex Kiderman is an employee of Neuro Kinetics, Inc. The remainder of the authors have no conflict of interest to declare. The views expressed herein do not necessarily reflect the official policy or position of the Department of the Navy, the Department of the Army, Department of Defense, or the U.S. Government. Dr. Kiderman's role was confined to device design and technical aspects of manuscript preparation and thus his employment by Neuro Kinetics, Inc. has no influence on the analysis, discussions, or conclusions of this manuscript.

Send correspondence to Michael E. Hoffer MD FACS, 1120 NW 14th Street, 5th Floor, Otolaryngology Department, Miami, FL 33136. E-mail: michael.hoffer@miami.edu

DOI: 10.1002/lio2.74

TABLE I.
Tests Performed Within the Oculomotor, Vestibular, and Reaction Time (OVRT) Test Battery.

Test	Variables
Optokinetic	Left and Right Gain and Asymmetry for nystagmus beats
Smooth Pursuit – Horizontal/Vertical	Percent of Saccadic Intrusions, Initiation Time
Saccade-Random – Horizontal/Vertical	Saccade Onset Latency, Accuracy, Peak Velocity, Area Under the Main Sequence Relationship
Predictive Saccade	Point in cycle at which subject anticipates/predicts the fixed timing interval and dot position as well as percent of correct predictions
Anti-saccade Horizontal	Number of Pro-saccadic errors, correct anti-saccades, Latency, and Velocity
Self-paced Saccade	Saccades per second
Gaze Horizontal	Vertical peak and average slow phase velocity
Visual Reaction Time	Mean and Standard Deviation (SD) of Latency
Auditory Reaction Time	Mean and SD of Latency
Saccade and Reaction Time	Saccade Onset Latency, Accuracy, and Latency and SD for motor responses
Computer Controlled Rotation Head Impulse Test (crHIT)	Left and Right Gain and Asymmetry
Sinusoidal Harmonic Acceleration (SHA)	Gain, Phase, and Asymmetry—High Frequencies
Visual Enhancement	Gain, Phase, and Asymmetry—High Frequencies
Visual Suppression	Gain, Phase, and Asymmetry—High Frequencies

standard for the diagnosis of mTBI has been described. Recently, investigators have described that neurosensory effects are the most common sequelae of mTBI. These disorders present a unique opportunity with respect to mTBI because they are almost universally present, they can be documented easily with qualitative and quantitative tests, and prompt treatment of these disorders can result in marked improvement and return to function. We have utilized this recognized connection to develop more objective tests that provide both diagnostic and prognostic testing. Working with Neuro Kinetics, Inc. (Pittsburgh, PA), we have discovered a combination of oculomotor, vestibular, and reaction time (OVRT) measures that can discriminate mTBI patients from control subjects.[1] These measures provide initial diagnostic accuracy of over 90%.

In this manuscript we expand upon this previous work and examine this group of subjects as they progress from an initial visit to subsequent visits at 7–10 days post injury and 14–17 days post injury. While still short term in nature, these time points give us a glimpse into the progression of mTBI/concussion over the initial acute and early subacute period of time. In particular, this study of a large group of subjects (106 mTBI and 300 controls) has provided an opportunity to study some important issues. This whole person analysis, incorporating OVRT test values and patient characteristics, allows us to correlate the OVRT test results with patient reports and symptoms (the current standard for the diagnosis of concussion in many acute and sub-acute care setting). Moreover, the analysis begins to provide important information about prognostic indicators provided by this new testing paradigm and how values at certain time points relate to longer-term status. This type of analysis allows us to begin to approach the important issue of when is it safe and appropriate to return to play/duty/work.

MATERIALS AND METHODS

This study was performed at 2 military hospitals and 1 civilian hospital. The study and the written informed consent and Health Information Portability and Accountability Act

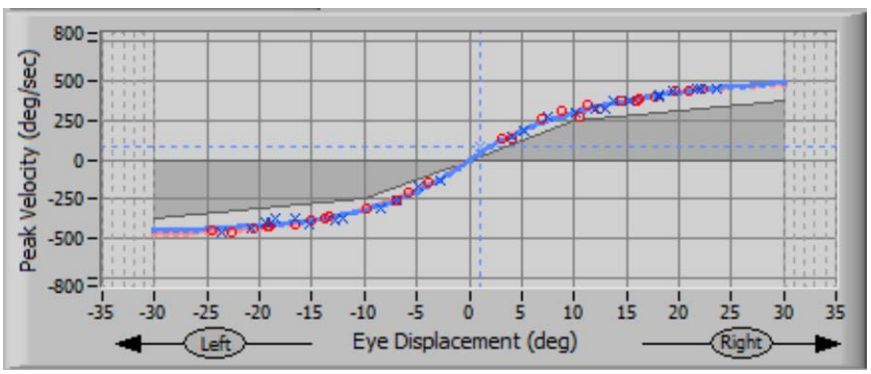

Fig. 1. Example of the saccade main sequence from a control subject. The fitted relationships are shown in blue for the left eye and red for the right eye. By convention, the rightward direction is positive. The average of the absolute values of the areas under the rightward and leftward curves was calculated as a metric of saccade main sequence performance.

TABLE II.
Demographic and Clinical Test Findings (Mean ± SD).

	No Concussion (Controls)		Concussion Session 1		Concussion Session 2		Concussion Session 3	
	Female (n = 95)	Male (n = 205)	Female (n = 34)	Male (n = 72)	Female (n = 32)	Male (n = 63)	Female (n = 31)	Male (n = 54)
Age	27.6 ± 6.9	27.3 ± 6.0	26.1 ± 6.1	26.2 ± 6.9	26.2 ± 6.2	26.2 ± 6.9	26.4 ± 6.3	27.0 ± 7.0
Time post-concussion (hr)			70.3 ± 44.3	59.3 ± 34.3	226.6 ± 72.3	213.9 ± 65.8	400.3 ± 78.6	398.3 ± 88.5
Symptom Score (22 minus number of symptoms)	19.9 ± 3.7	20.5 ± 2.6	8.4 ± 5.3	8.7 ± 6.5	8.8 ± 5.9	10.7 ± 7.5	12.5 ± 6.8	13.0 ± 8.0
Symptom Severity Rating (SCAT2)	3.4 ± 6.5	2.6 ± 5.4	42.3 ± 24.9	42.5 ± 29.6	35.7 ± 26.9	29.5 ± 27.2	25.4 ± 25.7	23.9 ± 27.8
FGA (≤22 fall risk)			25.1 ± 4.7 (5/34)	25.3 ± 4.6 (16/72)	26.5 ± 4.2 (2/32)	27.6 ± 3.3 (4/63)	28.1 ± 2.1 (1/31)	28.7 ± 2.1 (1/54)
TMT A			32.4 ± 13.1	29.0 ± 10.7	22.7 ± 6.6	24.8 ± 13.3	20.1 ± 5.7	21.2 ± 12.4
TMT B (49.8 ± 12.5 norms)			52.5 ± 23.5	56.2 ± 23.7	45.1 ± 16.9	52.1 ± 22.9	37.9 12.9	43.1 ± 20.7
DHI total (0:1-30:31-60:>60)			33.4 ± 22.3 (2:15:13:4)	30.4 ± 21.8 (6:37:22:7)	26.5 ± 23.0 (4:16:9:3)	22.1 ± 22.6 (16:26:16:5)	18.1 ± 21.9 (11:12:6:2)	17.6 ± 21.6 (19:23:9:3)

(HIPaA) documents were independently approved by the Institution Review Board (IRB) at the University of Miami, Naval Medical Center San Diego, and Madigan Army Medical Center. The IRB at the University of Pittsburgh independently approved de-identified data analysis.

The patient group was previously described,[1] with the exception of 6 additional mTBI subjects and 100 additional controls in this study. For easy reference, the subject group was composed of individuals between the ages of 18 and 45 who had a diagnosis of mTBI from the emergency room of one of the three recruitment sites. Mild traumatic brain injury was classified by the standard emergency medicine criteria including history of a head injury with neurosensory sequelae, a Glasgow Comma Scale of 14 or greater, and no loss of consciousness greater than 30 minutes. In the cases examined in this study these neurosensory symptoms included but were not limited to dizziness, hearing loss, headache, cognitive difficulties, and sleep disorders. Patients presented with a range of these symptoms with some have a single symptoms and some having multiple complaints. Additional inclusion criteria included the absence of a head injury 12 months prior to the current injury, the absence of any head injury symptoms prior to the current injury and never having been hospitalized for a head injury. Eligible individuals presented to the study center where they were again assessed for mTBI and the presence of any exclusion criteria. Those who were not excluded were offered participation in the study. All those who agreed signed written informed consent that was approved by the IRB of each institution. Control subjects were recruited from volunteers at the locations where the study was being conducted. These individuals were also between the ages of 18–45 and were screened to assure that they had no active medical condition and did not have any history of significant mTBI, ear, or balance disorders.

Full details of the methods of analysis are presented elsewhere.[1] For the readers' convenience the test battery of the OVRT testing is included in Table I.

The area under the saccadic main sequence relationship was calculated from analysis of Saccade Peak Velocity as a function of Saccade Amplitude during the random horizontal saccade task (Fig. 1). Two separate main sequences are built for leftward saccades and rightward saccades, fitted to the relationship:

$(\boldsymbol{x})=\boldsymbol{Ae}\text{^}(\boldsymbol{Bx})-\boldsymbol{A}$, where x is the Saccade Amplitude and y is the Saccade Peak Velocity.

Nonlinear regression least squares regression (Levenberg-Marquardt method) was used to estimate the A and B coefficients, and the area under the fit for 0–30 degree amplitude saccades was calculated as a gauge of main sequence robustness. In addition to these tests, a concussion symptom profile questionnaire (SCAT), a functional gait assessment (FGA), Trail

TABLE III.
Logistic Regression Coefficients for Control Versus mTBI Classification: Session 1.

	B	SE	Wald	df	Signif	Exp(B)
Antisaccade Task Overall Prosaccade Error Rate	.058	.013	20.884	1.000	.000	1.059
Chair delivered head impulse test (crHIT) Magnitude of vestibulo-ocular reflex (VOR) Gain Asymmetry	.763	.128	35.527	1.000	.000	2.146
Chair delivered head impulse test (crHIT) vestibulo-ocular reflex (VOR) Average Gain	−33.256	5.111	42.333	1.000	.000	0.000
Predictive Saccades, first predicted	.266	.052	26.525	1.000	.000	1.305
Magnitude of optokinetic nystagmus (OKN) Slow Phase Gain Asymmetry (20 d/s stimulus)	.123	.037	11.291	1.000	.001	1.131
Magnitude of Horizontal Smooth Pursuit Velocity Gain Asymmetry (0.75 Hz)	.083	.031	7.276	1.000	.007	1.087
Constant	23.691	4.442	28.442	1.000	.000	19444817670.000

mTBI = minor traumatic brain injury.

TABLE IV.
Progressions in Objective Classification of mTBI Subjects as Negative or Positive for mTBI, Based on Acute Test Battery Classifier in Table III.

Session 1 Class	Session 2 Class	Session 3 Class	Number
Negative	Negative	Negative	4
Negative	Positive	Negative	4
Positive	Negative	Negative	16
Positive	Positive	Negative	15
Positive	Positive	Positive	30
Positive	Negative	Positive	9
Negative	Positive	Positive	2
Negative	Negative	Positive	3

mTBI = minor traumatic brain injury.

Making Test (TMT) A and B, and a dizziness handicap inventory (DHI) was completed at each visit. The control subjects completed the SCAT as well.

RESULTS

Demographic data and test findings (mean ± standard deviation) for the FGA, TMTA and TMTB, and DHI are shown from the control and mild TBI groups in Table II. The male and female subjects did not differ in age across mTBI and control groups. Upon study entry in Session 1, there were no significant differences in these measures between the males and females with mTBI. There were no significant gender or gender X test metric interaction effects in Analysis of Variance (ANOVA) (repeated measures for sessions, gender as a between subjects factor). The FGA, TMTA, TMTB, and DHI scores improved significantly across sessions (both genders, repeated measures ANOVA, $p < .01$).

Acute Objective Classification of mTBI versus Control Subjects

Forward stepwise logistic regression analysis (Table III) revealed that 6 measures from five tests can classify the control and mTBI during Session 1 with a true positive rate (sensitivity) of 84.9% and true negative rate (specificity) of 97.0%. These measures are partially independent in the sense that they increment the sensitivity and selectivity in the analysis. The area under the Receiver-Operator Characteristic (ROC) curve was 0.9644. In-out samples (70/30%) cross-validation yielded 74.3% sensitivity and 96.0% specificity; leave-one-out cross-validation yielded 83.0% sensitivity and 97.0% selectivity (all at probe level of 0.5). The 5 predictive tests were: 1) computer-controlled head impulse test (2 parameters, velocity gain and absolute symmetry); 2) predictive saccade test (first saccade showing predictive response); 3) anti-saccade task (prosaccade performance error rate); 4) constant velocity optokinetic nystagmus (slow phase gain symmetry for 20 deg/s stimulation); and 5) horizontal smooth pursuit test (absolute velocity gain symmetry). The same logistic regression analysis on Session 2 yielded a sensitivity of 62.1% (59/95 subjects in the mTBI group), while the sensitivity declined to 53.0% (44/83 subjects in the mTBI group) on Session 3.

Among the 106 subjects with a diagnosis of mTBI at entry (Session 1), 95 returned for testing in Session 2 (14/16 of the subjects who were Test-Negative for mTBI in Session 1 and 81/90 subjects who were Test-Positive for mTBI in Session 1). Eighty-three of the subjects tested in Session 2 returned for testing 1 week later in Session 3 (32/36 Test-Negative individuals in Session 2 and 51/59 Test-Positive individuals from Session 2). The progression in test result patterns is shown in Table IV for the 83 tested in all sessions. To summarize, slightly fewer than half of the subjects (39/83, 47%) were classified by our 5 tests as mTBI-positive in both Session 1 and Session 3. On the other hand, 31/83 subjects (37.4%) were classified as mTBI-Positive during Session 1 and mTBI-Negative during Session 3. Among the 13 subjects who were classified

TABLE VI.
Demographic and Standard Assessment Data for Test Battery Results in Session 3 ($p < 0.05$).

	Acute Test Battery Results Session 3	
	mTBI Negative (n = 39)	mTBI Positive (n = 44)
Age	26.9 ± 6.3	26.1 ± 6.9
Time post-concussion (hr)	389.0 ± 62.6	399.7 ± 100.7
Symptom Score (22 minus number of symptoms)	14.7 ± 7.7	11.4 ± 6.9*
Symptom Severity Rating (SCAT2)	19.5 ± 24.7	27.0 ± 25.2
FGA (≤22 fall risk)	28.9 ± 1.6 (0)	28.2 ± 2.1 (1)
TMT A	20.1 ± 10.7	20.9 ± 9.6
TMT B (49.8 ± 12.5 norms)	42.3 ± 19.9	42.2 ± 18.9
DHI total (0:1-30:>31)	13.3 ± 20.5 (18:13:8)	21.1 ± 21.4 (12:21:11)

mTBI = mild traumatic brain injury, SCAT2 = sports concussion assessment Tool-2, FGA = functional gait assessment, TMT = trail making test, DHI = dizziness handicap inventory.

TABLE V.
Distribution of Predicted mTBI Status from Control Subjects and mTBI Subjects (Session 1 and Session 3 Data).

		Predicted Status from Session 3 OVRT tests			
Observed		mTBI Negative (cutoff < 0.4)	Possible mTBI (cutoff: 0.4–0.6)	mTBI Positive (cutoff > 0.6)	Total N
No mTBI	Control	290 (96.7%)	4 (1.3%)	6 (2%)	300
mTBI	Session 1 Data	15 (14.1%)	6 (5.7%)	85 (80.2%)	106
	Session 3 Data	32 (38.6%)	14 (16.9%)	37 (44.6%)	83

mTBI = minor traumatic brain injury.

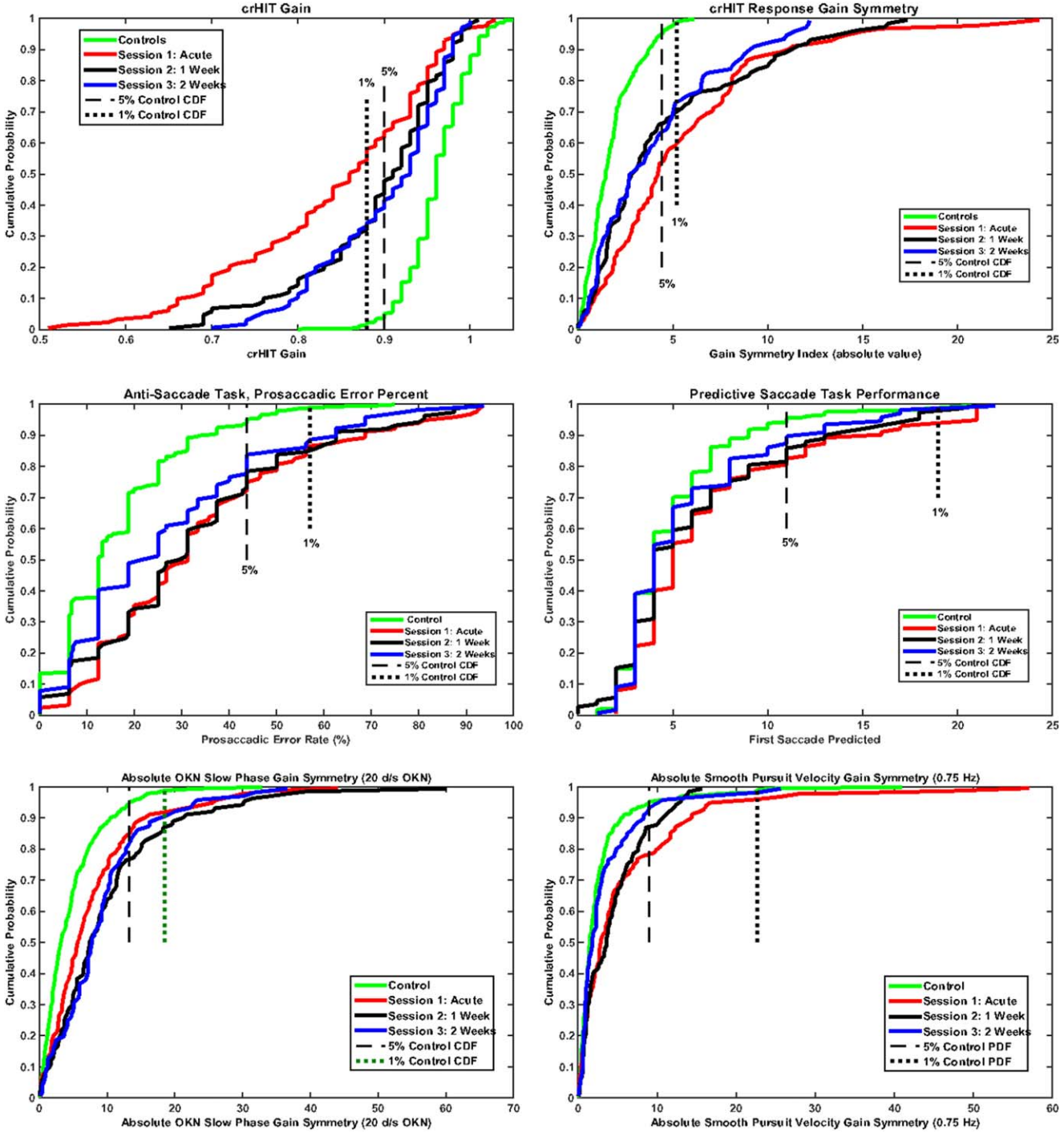

Fig. 2. Cumulative distribution functions for tests that predicted mTBI status during the acute testing period (Session 1). The 5% and 1% points for the control population are indicated by vertical lines. mTBI = minor traumatic brain injury.

as mTBI-negative in Session 1, 8 were classified as mTBI-Negative and 5 as mTBI-positive in Session 3. Among the mTBI group, females (12/31) and males (27/52) did not differ in the likelihood of being classified as mTBI-negative in Session 3 (Fisher exact test, $p > .25$). All but one of the subjects classified as mTBI-positive in Session 3 had at least 1 test result that was a 5% outlier to the control data set. The remaining subject was worse than the 10% outlier range for 5 of the 6 metrics.

The default cutoff for classification by standard logistic regression is a membership probability of 0.5. Another clinically relevant approach is to classify the subjects into three groups: a predicted control test performance (cutoff less than 0.4), a predicted mTBI test performance (cutoff greater than 0.6) and a predicted "suspect performance" (cutoff of 0.4–0.6) group. The shift in proportions of mTBI subjects toward a negative test classification (i.e., predicted as "no mTBI") during Session

TABLE VII.
Prevalence of Extreme Test Measures (300 Control Subjects) in the Tests Identified by the Session 1 Logistic Regression Classification.

5% and 1% tail outliers from controls entered	Session 1	Session 2	Session 3
crHIT average VOR gain	65/106 (61.3%)	41/95 (43.2%)	32/83 (38.6%)
	54/96 (50.9%)	28/95 (29.5%)	25/83 (30.1%)
crHIT, absolute VOR gain Symmetry	49/106 (46.2%)	32/95 (33.7%)	31/83 (37.4%)
	41/106 (38.7%)	28/95 (29.5%)	22/83 (26.5%)
Prosaccadic Error % in Anti-saccade Task	26/106 (24.5%)	20/95 (21.1%)	13/83 (15.7%)
	14/106 (13.2%)	14/95 (14.7%)	10/83 (12.1%)
First Predicted Saccade	18/106 (17.0%)	13/95 (13.7%)	8/83 (9.6%)
	6/106 (5.7%)	2/95 (2.1%)	1/83 (1.2%)
OKN Slow Phase absolute velocity gain symmetry (20 deg/s stimulus)	16/106 (15.1%)	22/95 (23.2%)	15/83 (18.1%)
	9/106 (8.5%)	12/95 (12.6%)	8/83 (9.6%)
Horizontal Smooth Pursuit absolute velocity gain symmetry	23/106 (21.7%)	12 (12.6%)	6 (7.2%)
	4/106 (3.8%)	0	1 (1.2%)

3 was highly significant (exact test, $p < .001$), reflecting nearly a tripling of the proportion with a negative or "Possible mTBI" test result and roughly a halving of the proportion showing positive signs (Table V).

The demographic and basic test data are summarized in Table VI for subjects who were classified in Session 3 (as mTBI-Positive or mTBI-Negative) by the acute logistic regression-based classifier. The symptom scores from the SCAT were significantly less severe in subjects identified by the OVRT panel as mTBI-negative ($p < .05$). The Symptom Severity Score and DHI showed trends in the same direction, but were not significantly different. The FGA and the TMT had normalized in the subjects by Session 3. Thus, classification by the test for acute identification is consistent with symptom scales, DHI, FGA, and TMT in reflecting clinical improvement at two weeks after the traumatic event.

The amelioration of the performance on these measures in the mTBI population are evident in alterations in the cumulative distribution functions across sessions (Fig. 2). Individual plots show the mTBI subject data relative to the locations of the extreme 5% and 1% tails of the control subjects. Table VII shows the prevalence of subjects in the extreme 5% and 1% ranges of the control observations at each test session. The high prevalence of individuals with computer controlled head impulse test (crHIT) mean gain in the lowest 5% of the control distribution and of individuals with the other metrics in the upper 5% of the control distribution reflect the inclusion of these measures in the result from the forward stepwise logistic regression algorithm. The prevalence of extreme test scores decreased for the later sessions, paralleling the decrease in positive classification for mTBI at those times.

There was a dramatic normalization of performance on the battery of 6 metrics for acute mTBI (Session 1) in the mTBI subjects who were classified as negative during Session 3 (Fig. 3). The cumulative distribution functions of the subjects classified as negative converged toward the distribution functions from the control group. The group classified as positive, though, showed complete recovery of a control cumulative distribution function on only one measure, horizontal smooth pursuit gain symmetry (0.75 Hz). Hence, logistic regression gives perfect classification of Positive-Negative Session 3 status with 6 metrics from 5 tests: 2 crHIT measures, OKN slow phase gain symmetry 20 deg/s, anti-saccade error rate, and the first predicted saccade in the predictive saccade task.

A second logistic regression analysis (forward stepwise regression with a Wald criterion) was performed on the test results from Session 3 to examine whether longer term signs were emerging in the mTBI group within 2 weeks after initial testing (an average of more than 16 days post-mTBI, see Table II). The analysis (Table VIII) included the metrics that predicted mTBI status in the first, acute session. As expected from the distribution functions in Figures 1 and 2, the 2 crHIT measures remained as distinguishing metrics. However, two other measures emerged to assist in identifying as positive 50/83 (60.2%) of the subjects from the Session 1 mTBI group from 96.7% negative for the control group. If the adopt a cutoff criterion of less than 0.4 for a definite negative finding and greater than 0.6 for a positive classification, then 31/83 (37.3%) were definitely negative by this metric in Session 3, 42/83 (50.6%) of the mTBI group were classified as definitely positive, and 10/83 (12%) remained as possible mTBI. The cumulative distribution functions of the phase of the horizontal VOR during 0.64 Hz sinusoidal oscillation and the mean area under the main sequence curve for horizontal saccades (0–30 degree magnitudes) shifted further from the control group distribution between Sessions 1 and 3. (Fig. 4) However, there were no significant differences in symptom scores, DHI, FGA, or TMT times between the groups classified by this regression.

DISCUSSION

We have previously described that a small battery of 3 OVRT tests can help distinguish acute mTBI patients from controls with a high degree of accuracy. This communication focuses on a longer term analysis of an augmented sample size, with the addition of 100 control subjects and 6 subjects with mTBI. This larger control sample

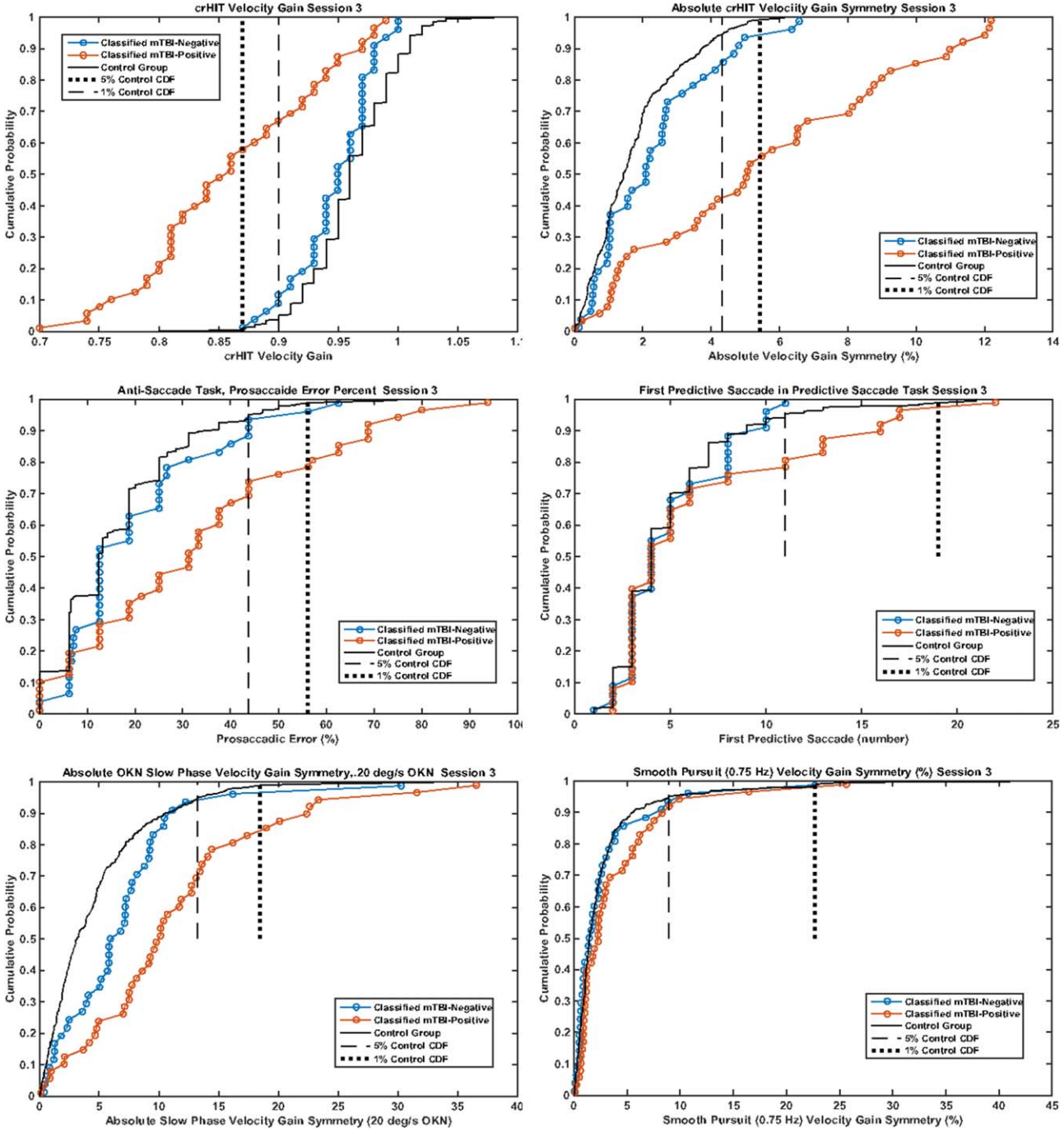

Fig. 3. Cumulative Session 3 distribution functions of individual test metrics from subjects with mTBI during Session 1. The subjects with Session 3 mTBI-positive logistic regression scores are plotted in red and subjects with mTBI-negative scores in blue. The Control group cumulative distributions functions are plotted for comparison. mTBI = minor traumatic brain injury.

allowed us to expanded the critical test from 4 to 6 measures (from 5 tests): 1) crHIT velocity gain, 2) crHIT absolute symmetry, 3) predictive saccade test (first saccade showing predictive response), 4) anti-saccade task (prosaccade performance error rate), 5) constant velocity optokinetic nystagmus (slow phase gain symmetry for 20 deg/s stimulation), and 6) horizontal smooth pursuit test (absolute velocity gain symmetry). Improvement in performance on these tests was associated with recovery within 2 weeks of presentation. Normal logistic regression scores were observed in 47% of the mTBI subjects approximately 2 weeks after injury, reflecting the normalization of the individual test scores to the distribution of the control subjects. The patients with normalized regression scores had has significantly better symptom scores relative to those identified by logistic regression as positive for mTBI at that 2 week post-injury session. This latter finding confirms that the scores improve with recovery,

TABLE VIII.
Results of Logistic Regression for Session 1 Concussion Status on Session 3 Tests.

	B	SE	Wald	Df	Signif	Exp(B)
crHIT Magnitude of VOR Gain Asymmetry	0.395	0.098	16.226	1	<0.001	0.999
crHIT VOR Average Gain	−19.294	3.786	25.965	1	<0.001	.000
Horizontal Saccades, mean absolute area under main sequence	0.001	0.000	25.289	1	<0.001	0.999
Sinusoidal Harmonic Oscillation, phase angle, 0.67 Hz	−0.162	0.034	22.427	1	<0.001	0.850
Constant	23.341	3.926	35.339	1	<0.001	13703769250.0

but little is known about the trajectories of objective signs from acute to subacute to chronic mTBI. Hence, a second stepwise regression was performed to explore whether new signs were emerging within the first 2 weeks of the subacute period. The 2 crHIT measures remained predictive of an initial mTBI. Two other measures also emerged: 1) the phase of the horizontal VOR during 0.64 Hz sinusoidal oscillation and 2) the mean area under the main

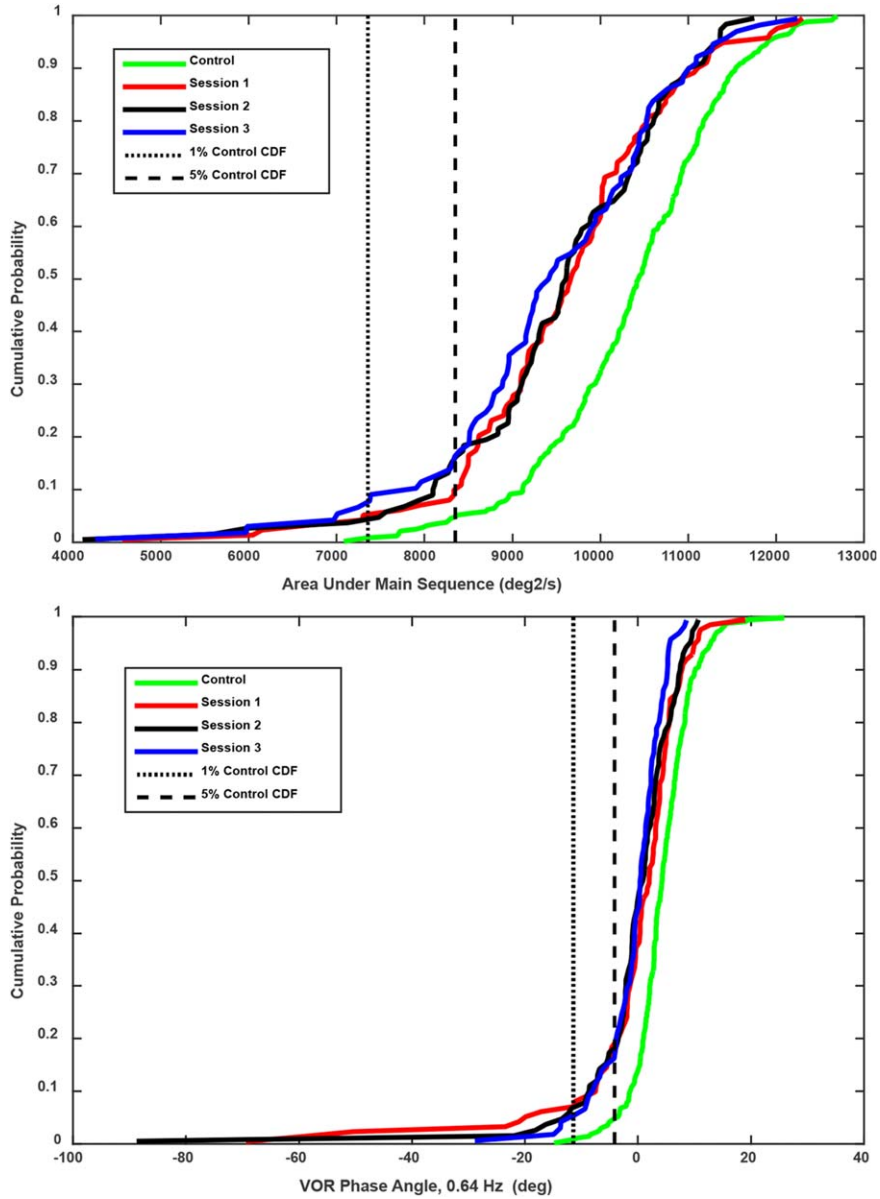

Fig. 4. Cumulative distribution functions after mTBI of the area under the saccadic main sequence and the VOR phase angle at 0.64 Hz horizontal oscillation. Note the persistence of an increased proportion of outliers during Session 3. mTBI = minor traumatic brain injury, VOR = vestibulo-ocular reflex.

sequence curve for horizontal saccades (0–30 degree magnitudes). The former measure remained at the Session 1 level, while the area under the saccade main sequence metric shifted further from the control cumulative distribution between Sessions 1 and 3. The latter finding suggests a subtle but persistent reduction in saccade motor performance in a proportion of mTBI subjects.

The fact that the same OVRT measurements are useful in assessing the patients with physician-identified mTBI within 2 weeks of injury is not surprising. The persistence of the acute findings further supports the importance of these objective performance metrics as tests for mTBI-induced dysfunction. Because these metrics are relative to control population norms, they do not require prior baseline testing. It also makes sense that other tests (e.g., saccade main sequence metrics) may emerge in some patients in the subacute to chronic time frame. However, longer follow-up times will be needed in future studies to identify the trajectories to chronic mTBI.

The diagnosis and treatment of mTBI suffers from several inherent limitations. This heterogeneous disorder has a varying array of symptoms that can change over time. Even the initial presentation can be different for individuals exposed to largely the same impact not to mention the effects of different impact and the sum total of any previous injury. Genetics likely plays a large role to outcomes as well. The disorder is further plagued by current diagnostic and prognostic tools that rely on a baseline testing (that may or may not be altered by the participants intentions), self report (that is inherently inaccurate), and/or a set of test modalities that many individuals could pass even when injured. These first generation tests remain the standard of care for diagnosing mTBI/concussions today and for making recommendations about return to activity. Most of those working in this field agree that better diagnostic and prognostic algorithms and tools need to be developed. We have described, in this manuscript, a new second generation of testing that has several critical advantageous over previous tests as follows: 1) It does not rely on baseline testing; 2) It is objective and not subject to the participants desired outcome; 3) It is quick (the portable version can be performed in five minutes); and 4) It can be made scalable for use at the point of injury, in the emergency room, or in any provider's office.

The development of a second generation test shown in the manuscript will allow us and other investigators to move this science forward. Work is underway in our lab to test a portable version of this test and comparable outcomes have already been demonstrated. More work needs to be done examining other groups of patients, longer outcomes, and the best return to activity test outcomes.

CONCLUSIONS

This paper expands upon the work we previously reported confirming the acute measures that were shown to be diagnostic for mTBI with a high degree of accuracy. These same measures can be used to follow individuals into the subacute time period and that normalization of these measures correlates with symptom resolution. We also describe additional measures that might be useful for examining the development of a more chronic symptom pattern. We believe this work represents an introduction to a second generation of mTBI/concussion testing and will lead to the introduction of point of injury devices for use on the sidelines or an office setting. Just such a device is already being studied in our laboratory and the labs of our collaborators.

BIBLIOGRAPHY

1. Balaban C, Hoffer ME, Szczupak M, et al. Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. *PLoS One* 2016;11: e0162168. doi:10.1371/journal.pone.0162168.
2. Hoffer ME, Szczupak M, Kiderman A, et al. Neurosensory symptom complexes after acute mild traumatic brain injury. *PLoS One* 2016;11:???–???.
3. Hoffer ME, Balaban C, Gottshall K, Balough BJ, Maddox MR, Penta JR. Blast exposure: vestibular consequences and associated characteristics. *Otol Neurotol* 2010;31:232–236.
4. Scherer MR, Burrows H, Pinto R, et al. Evidence of central and peripheral vestibular pathology in blast-related traumatic brain injury. *Otol Neurotol* 2011;32:571–580.
5. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N Engl J Med* 2008;358:453–463.
6. Terrio H, Brenner LA, Ivins BJ, et al. Traumatic brain injury screening: preliminary findings in *a US Army Brigade Combat Team. J Head Trauma Rehabil* 2009;24:14–23.
7. Centers for Disease Control and Prevention. Injury Prevention & Control: Traumatic Brain Injury & Concussion [on-line]. February 9, 2016. Available at: http://www.cdc.gov/TraumaticBrainInjury/index.html. Accessed October 31, 2016.
8. Hosek B. How is deployment to Iraq and Afghanistan affecting U.S. service members and their families? An overview of early RAND research on the topic. Santa Monica, CA: RAND Corporation; 2011.
9. Powell JW, Barber-Foss KD. Traumatic brain injury in high school athletes. *JAMA* 1999;282:958–963.
10. Guerrero JL, Thurman DJ, Sniezek JE. Emergency department visits associated with traumatic brain injury: United States, 1995–1996. *Brain Inj* 2000;14:181–186.
11. Kerr ZY, Harmon KJ, Marshall SW, Proescholdbell SK, Waller AE, The epidemiology of traumatic brain injuries treated in emergency departments in North Carolina, 2010–2011. *N C Med J* 2014;75:8–14.
12. Marin JR, Weaver MD, Yealy DM, Mannix RC. Trends in visits for traumatic brain injury to emergency departments in the United States. *JAMA* 2014;311:1917–1919.
13. Lagbas C, Bazargan-Hejazi S, Shaheen M, Kermah D, Pan D. Traumatic brain injury related hospitalization and mortality. *California Biomed Res Int* 2013:143092.
14. Olson D, Sikka RS, Labounty A, Christensen T. Injuries in professional football: current concepts. *Curr Sports Med Rep* 2013;12:381–390.
15. Poltavski DV, Biberdorf D. Screening for lifetime concussion in athletes: importance of oculomotor measures. *Brain Inj* 2014;28:475–485.
16. Harmon KG, Drezner JA, Gammons M et al. American Medical Society for Sports Medicine position statement: concussion in sport. *Br J Sports Med* 2013;47:15–26.
17. Marar M, McIlvain NM, Fields SK, Comstock RD. Epidemiology of concussions among United States high school athletes in 20 sports. *Am J Sports Med* 2012;40:747–755.