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

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**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 2 weeks 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

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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. 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 it is 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

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

| Test Measure                        | 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 ± 6.9               |                      | 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         |
|                                     | 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 Score (22 minus number of symptoms) | 19.9 ± 3.7               | 20.5 ± 2.6           |                      |                      |
|                                     | 3.4 ± 6.5                | 2.6 ± 5.4            |                      |                      |
| Symptom Severity Rating (SCAT2)     | 25.1 ± 4.7               | 25.3 ± 4.6           | 26.5 ± 4.2           | 27.6 ± 3.3           |
|                                     | (5/34)                   | (16/72)              | (2/32)               | (4/63)               |
|                                     | 28.1 ± 2.1               | 28.7 ± 2.1           |                      |                      |
| FGA (<22 fall risk)                 | 32.4 ± 13.1              | 29.0 ± 10.7          | 22.7 ± 6.6           | 24.8 ± 13.3          |
|                                     | (16/26:16:5)             |                      | (7/26)               | (11/26:16)           |
|                                     | 20.1 ± 5.7               | 21.2 ± 12.4          |                      |                      |
| TMT A (49.8 ± 12.5 norms)           | 52.5 ± 23.5              | 56.2 ± 23.7          | 45.1 ± 16.9          | 52.1 ± 21.9          |
|                                     | (2/15:13:4)              | (6:37:22:7)          | (4:16:9:3)           | (11:12:6:2)          |
|                                     | 37.9 ± 12.9              | 43.1 ± 20.7          |                      |                      |
| TMT B (49.8 ± 12.5 norms)           | 33.4 ± 22.3              | 30.4 ± 21.8          | 26.5 ± 23.0          | 22.1 ± 22.6          |
|                                     | (2:15:13:4)              | (6:37:22:7)          | (4:16:9:3)           | (11:12:6:2)          |
|                                     | 18.1 ± 21.9              | 17.6 ± 21.6          |                      |                      |
| DHI total (0:1-30:31-60:60)         | 24.9 ± 42.5              | 22.9 ± 10.7          | 22.7 ± 6.6           | 24.8 ± 13.3          |
|                                     | (7:16:26)                |                      | (7/26)               | (11/26:16)           |
|                                     | 20.1 ± 5.7               | 21.2 ± 12.4          |                      |                      |

(HPaA) documents were independently approved by the Institutional 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, 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 having a single symptom 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. 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 and rightward saccades, fitted to the relationship:

\[ y = A + Bx \]

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 of Saccade Amplitude during the random horizontal saccade task (Fig. 1). Two separate main sequences are built for leftward and rightward saccades, fitted to the relationship:

\[ y = A + Bx \]

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 of 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.

| Test Measure                                           | 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 | -.33256 | 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 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...
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

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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 step-wise 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
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 (pro-saccade 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 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.
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 sequence.

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

| Measure                                                                 | 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 | 0.000  |
| 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 |

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 or 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.

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