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TITLE: Pupillometry and Saccades as Objective mTBI Biomark

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13. SUPPLEMENTARY NOTES mild traumatic brain injury (mTBI), infrared pupillometers, King-Devick (KD) test, near point of convergence (NPC) rule, objective biomarkers					
14. ABSTRACT The objective of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for the identification of Warfighters with acute mild traumatic brain injury (mTBI) using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively. Hundred mTBI and 100 age-matched non-TBI (controls) military personnel are to be recruited from the patient population at Womack Army Medical Center (WAMC). This study was designed determine within each group the effectiveness of these tests, individually and/or in combination, to correctly identify mTBI in agreement with the mTBI diagnosis made by the WAMC Department of Brain Injury Medicine. Preliminary results showed that three of the eight PLR parameters are statistically different between the groups: average constriction velocity, average dilation velocity, and 75% dilation recovery time. In addition, the KD test, NPC rule, and the CISS survey showed sensitivity in identifying military personnel with mTBI.					
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INTRODUCTION:

The DOD reported that 333,169 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.4% (DVBIC 2015). The diagnosis of mTBI has been a challenge for the military primarily because of the lack of objective assessment tools, overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD), and the interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters (Marion 2011). The objective of the study is to validate pupillary light reflex (PLR), saccadic and convergence eye movements as objective biomarkers for the identification of Warfighters with acute mTBI using commercial-off-the-shelf (COTS) instruments: infrared pupillometers, King-Devick (KD) test and near point of convergence (NPC) rule, respectively. Hundred acute mTBI (≤ 72 hrs post injury) and 100 age-matched non-TBI (controls) military personnel will be recruited from the patient population at Womack Army Medical Center (WAMC). This study was designed determine within each group the effectiveness of these tests, individually and/or in combination, to correctly identify mTBI in agreement with the mTBI diagnosis made by the WAMC Brain Injury Medicine Department. There are five hypotheses being tested. First, those who have suffered acute mTBI/concussion will have abnormal PLR findings in comparison to controls. Second, those who have suffered acute mTBI/concussion will have abnormal KD test score in comparison to controls. Third, those who have suffered acute mTBI/concussion will have receded NPC compared to controls. Fourth, those who have suffered acute mTBI/concussion will have higher Convergence Insufficiency Symptoms Survey (CISS) scores in comparison to controls. Fifth, the PLR values measured by the PLR-200 pupillometer (research grade) are not different to those measured by the NPi-100 pupillometer (clinic grade).

BODY:

Major Task 1: Administrative Requirements

Subtask 1: Hire Optometrist and Ophthalmic Assistance: COMPLETED

The Geneva Foundation recruited and hired the Research Optometrist and the Ophthalmic Assistant required for the study within the first quarter of the performance period. In addition, research staff completed all research and WAMC level training required to conduct the study within the first quarter of the performance period.

Subtask 2: Purchase equipment and supplies: COMPLETED

The Geneva Foundation purchased supplies, equipment and electronic devices required to collect, store, and analyze research data within the first quarter of the performance period.

Subtask 3: WAMC IRB approval: COMPLETED

The study protocol received approval by WAMC Institutional Review Board (IRB) within the first quarter of the performance period.

Subtask 4: USAMRMC HRPO approval: COMPLETED

The study protocol received approval by US Army Medical Research and Materiel Command (USAMRMC) Human Research Office Protection (HRPO) within the first quarter of the performance period.

Major Task 2: Data Collection on Military Personnel at WAMC

Subtask 1: Procedures and data collection training/standardization: COMPLETED

Research staff was training on study procedures and data collection standardization during the first quarter of the performance period. Procedures standardized prior to initiation of the study included: PLR-200 and NPi-100 monocular pupillometers, KD test, NPC rule, and CISS Questionnaire.

Subtask 2: Complete data collection in 100 subjects with mTBI: IN PROGRESS

Complete data set have been collected for 95 acute mTBI subjects (84 males and 11 females; age range 19-49). Five subjects remaining to complete this subgroup. No problems expected to recruit and complete data collection of acute mTBI during the second year of the performance period.

Subtask 3: Complete data collection in 100 age-matched control subjects (non-TBI): IN PROGRESS

Complete data set have been collected for 73 age-matched control subjects (57 males and 16 females; age range 18-49). Twenty-seven subjects remaining to complete this subgroup and initiate comprehensive age-matched data analysis. No problems expected to recruit and complete data collection of age-matched controls during the second year of the performance period.

Major Task 3: Data Analysis and Report Writing

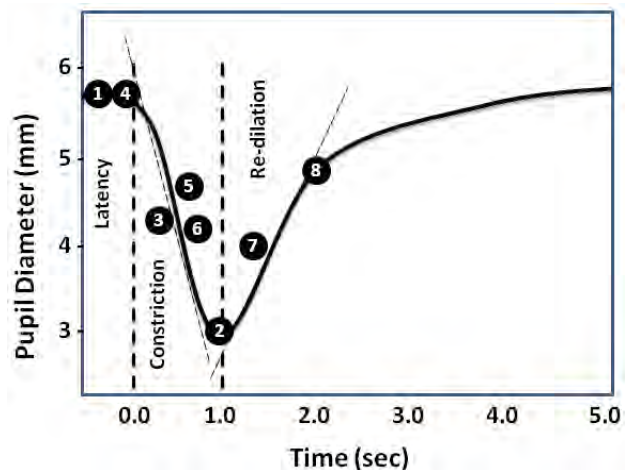
Subtask 1: Complete progress report: COMPLETED

WAMC IRB and USAMRMC HRPO approved the study protocol continuing review on 13 March 2015 and 30 March 2015, respectively. Quarterly reports (n = 3) have submitted to Contract Specialist, U.S. Army Medical Research Acquisition Activity and Science Officer, Congressionally Directed Medical Research Programs, USAMRMC, following the timeline indicated in the contract.

Subtask 2: Complete data analysis: PRELIMINARY ANALYSIS COMPLETED

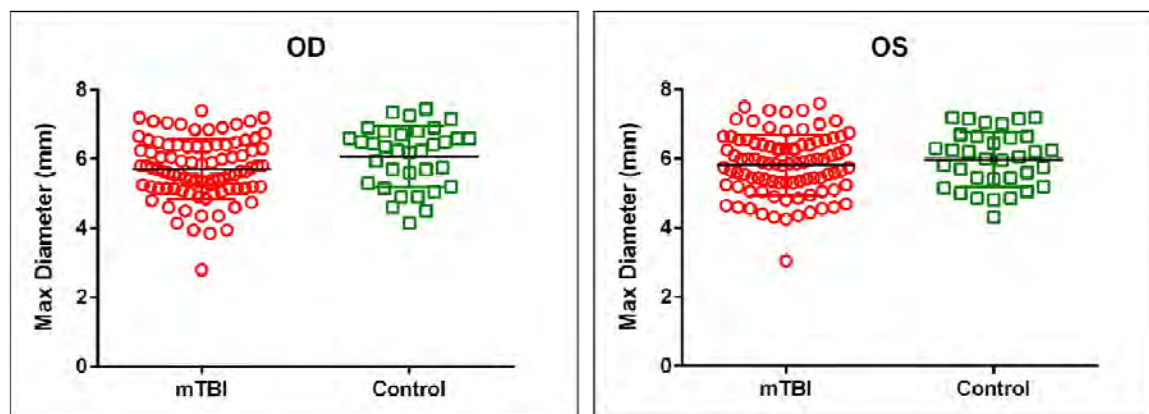
All subjects were corrected to 20/20 and had similar spherical equivalent refractive error (mTBI -0.49 ± 2.07 D; non-TBI $+0.12 \pm 0.98$ D; $p = 0.25$). All subjects, in both groups, had normal pupil response and no afferent pupil defect with the manual penlight examination. Pupillary light reflexes (Figure 1) and oculomotor functions can be affected by age; therefore, an accurate data

Figure 1. Schematic diagram of the pupillary reaction curve illustrating PLR recorded parameters: 1) maximum diameter; 2) minimum diameter; 3) percent of constriction; 4) constriction latency; 5) average constriction velocity; 6) maximum constriction velocity; 7) average dilation velocity; 8) 75% recovery time.

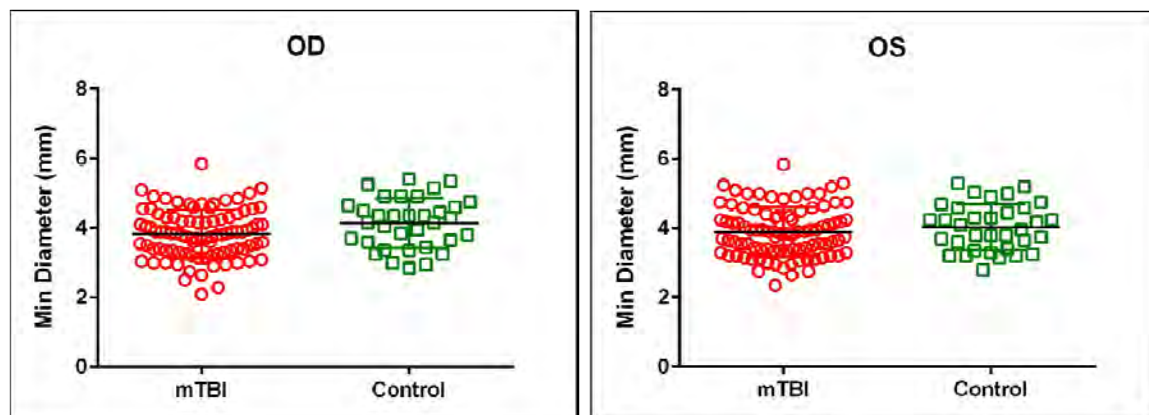


analysis requires to age-match the experimental (mTBI) and the control subjects. However, a preliminary non age-match analysis was completed to evaluate the initial data and to present preliminary results at the WAMC Annual Research Symposium here in Fort Bragg on 6 May 2015 (Appendix). The preliminary results compared monocular (right eye (OD; left eye (OS)) PLR of 91 Service members with mTBI during the acute stage (≤ 72 hrs) post injury and 34 age-matched controls who had neither experienced an mTBI nor been exposed to a blast event. The initial analysis showed that following results:

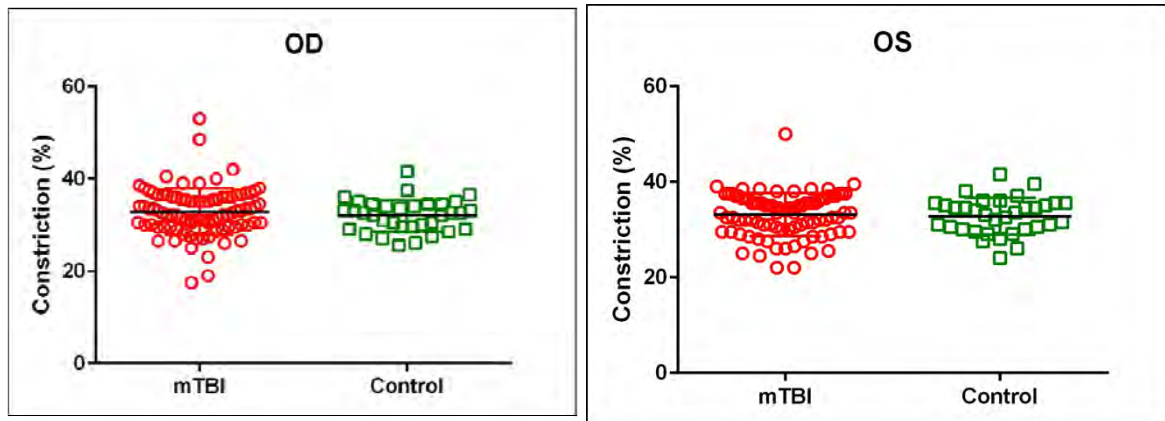
- 1) Maximum pupil diameter showed no significant difference between the acute mTBI and control group (OD $P = 0.25$; OS eye $P = 0.32$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013).



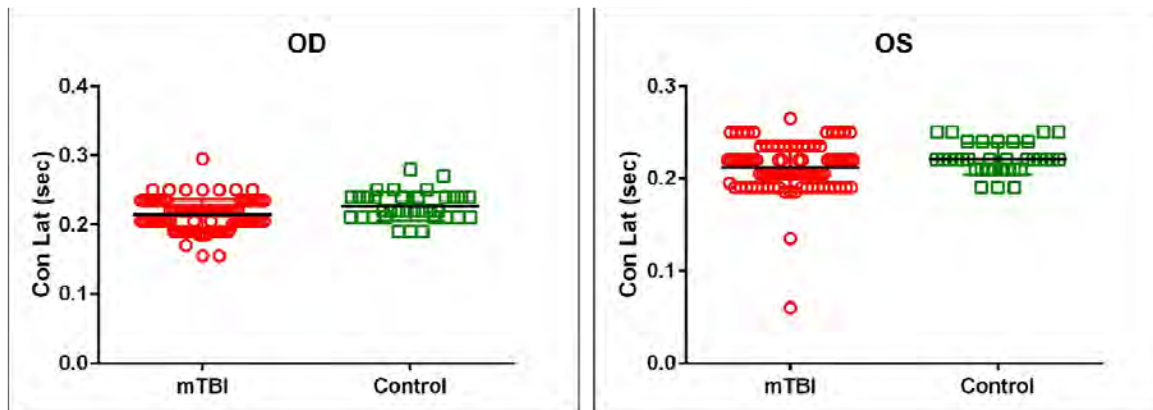
- 2) Minimal pupil diameter showed no significant difference between the acute mTBI and control group (OD $P = 0.15$; OS $P = 0.33$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013).



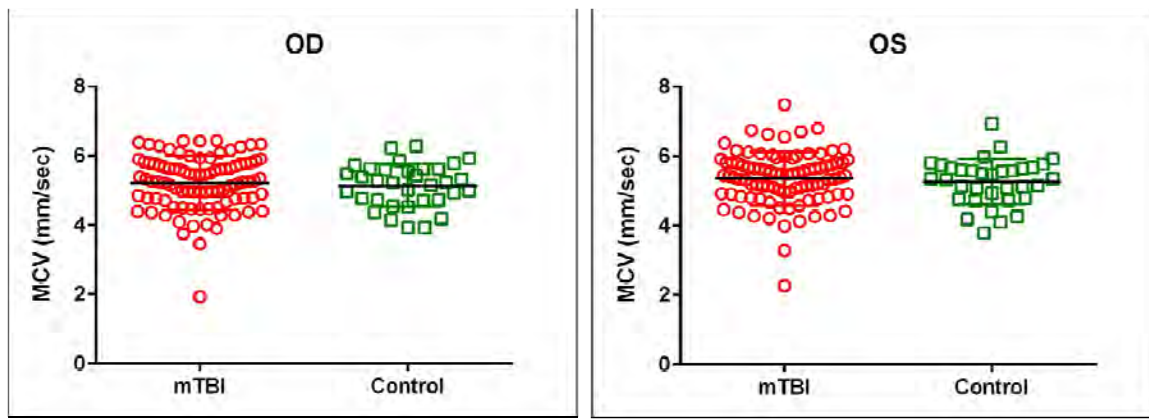
- 3) Percent of pupil constriction showed no significant difference between the acute mTBI and control group (OD $P = 0.38$; OS $P = 0.66$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013).



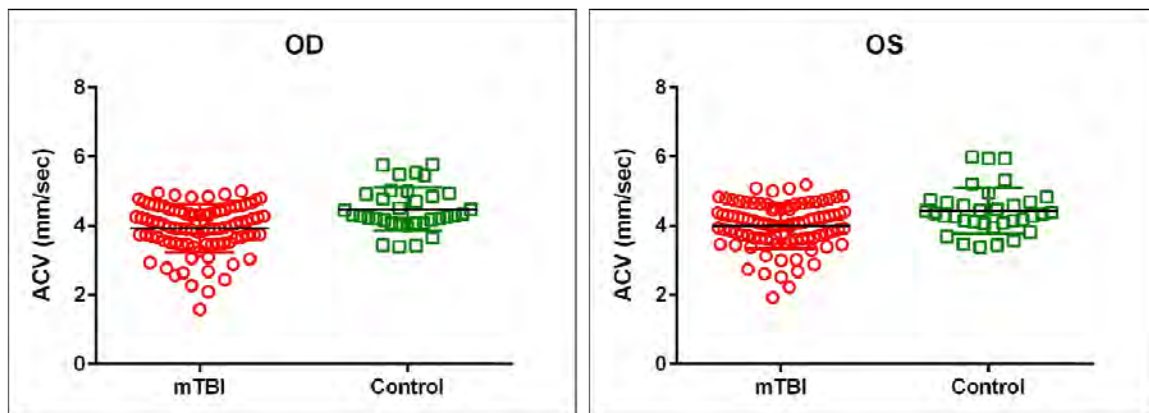
- 4) Constriction Latency (Con Lat) for the preliminary findings did not show a statistical difference (OD $P = 0.055$; OS $P = 0.059$), see figure below. This is inconsistent with the only pupillometry study in the literature (Capo-Aponte 2013); however, the results were just shy from the statistical significance set at 0.05. Incomplete sample size may account for this between study discrepancy in statistical significance.



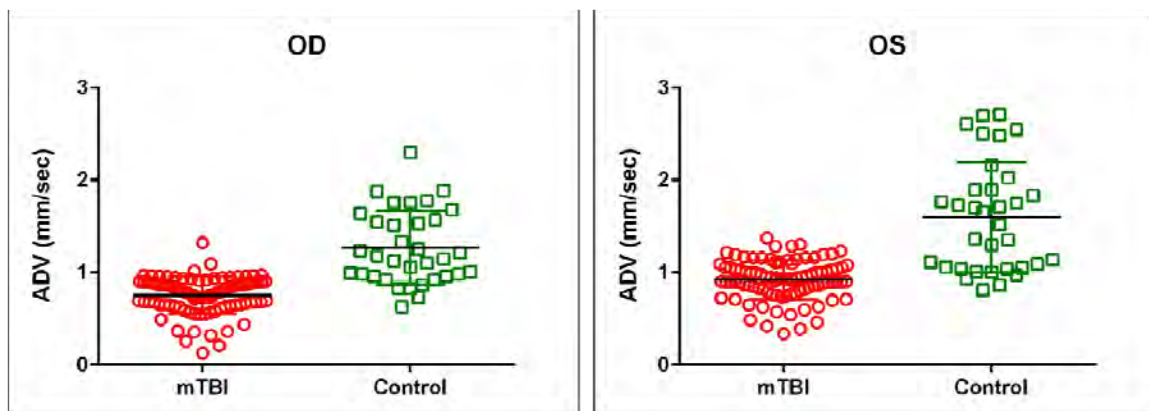
- 5) Maximum constriction velocity (MCV) for the preliminary findings did not have between groups statistical difference (OD $P = 0.25$; OS $P = 0.32$), see figure below. These results are consistent with a previous published study comparing subacute (15-45 days post injury) using the same instrument (i.e., Neuroptics PLR-200) (Capo-Aponte, 2013).



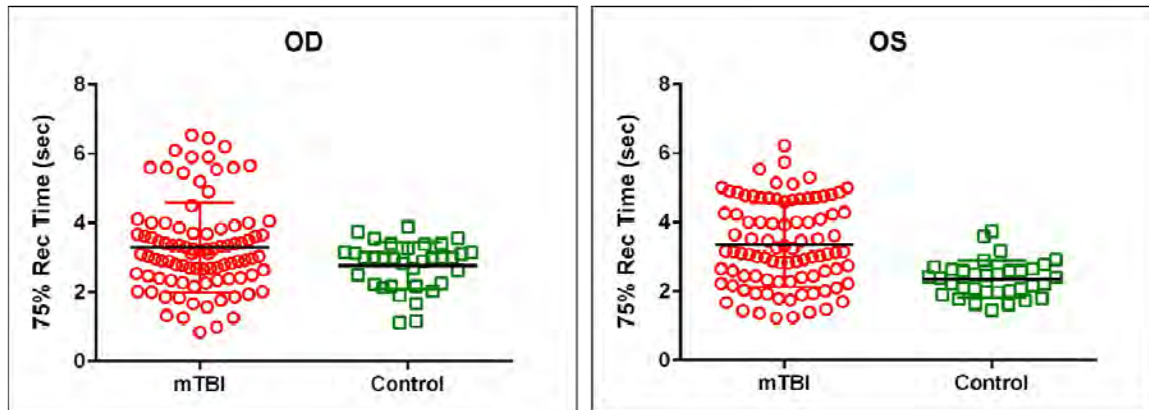
- 6) Average Constriction velocity is significantly reduced in mTBI subjects mTBI (OD $P < 0.001$; OS $P = 0.003$), see figure below. This is in agreement with a previous study (Capo-Aponte 2013).



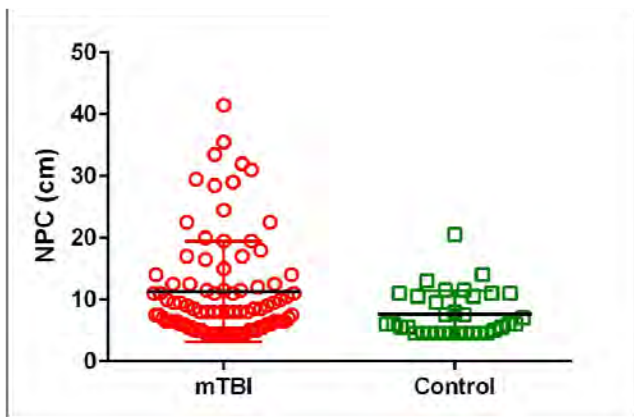
- 7) Average dilation velocity (ADV) is significantly reduced in mTBI subjects mTBI (OD $P < 0.001$; OS $P < 0.001$), see figure below. This is in agreement with a previous study (Capo-Aponte 2013).



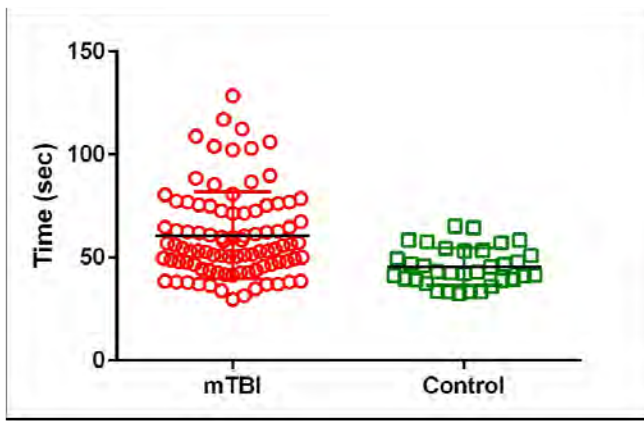
- 8) The total time taken by the pupil to recover 75% of the initial resting pupil size after it reached the peak of constriction is significantly longer in mTBI group (OD $P < 0.001$; OS $P = 0.025$), see figure below. This is in agreement with a previous study (Capo-Aponte 2013).



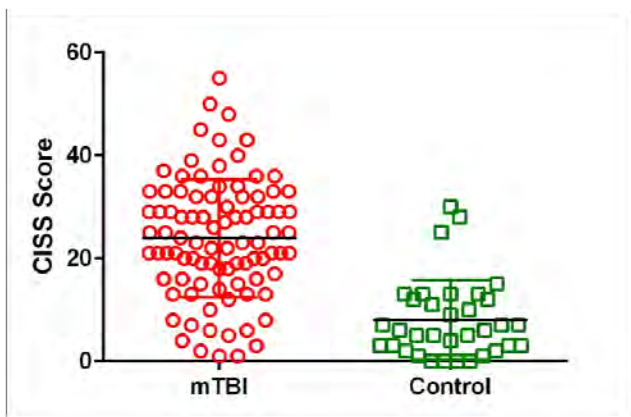
- 9) mTBI group had a significantly reduced NPC compared to the control group ($P < 0.001$), see figure below. Normal NPC values are up to 10 cm.



- 10) The KD test is used to evaluate saccadic eye movement. The KD test is based on measurement of the speed of rapid number naming and involves reading aloud a series of single-digit numbers from left to right on three test cards. KD test showed significantly longer performance time for mTBI group compared to the control group. The expected mean time (sec) for the KD test are: pass < 45 ; borderline 45-60; fail > 60 .



11) The CISS documents the frequency of visual symptoms. Each symptom question had five possible answers with an associated value, where 4 = always, 3 = frequently, 2 = sometimes, 1 = rarely, and 0 = never. Thus, the cumulative symptoms score can vary from 0 to 60. An average normal adult should score <21 points. There was a significantly higher score on CISS score for the mTBI group ($P < 0.001$), see figure below.



Subtask 3: Complete final report: NO INITIATED (Schedule for 2nd performance Yr)

KEY RESEARCH ACCOMPLISHMENTS:

- Received initial protocol and continuing review approval by WAMC IRB
- Received initial protocol and continuing review approval by USAMRMC HRPO
- Collected Data in 95 mTBI subjects (95% completion)
- Collected Data in 73 age-matched control subjects (73% completion)
- Presented preliminary results at the WAMC Annual Research Symposium (Appendix May 2015)

REPORTABLE OUTCOMES:

- Presentation of preliminary results at the WAMC Annual Research Symposium (Appendix).

CONCLUSION:

Preliminary results showed that three of the eight PLR parameters are statistically different between the groups: average constriction velocity, average dilation velocity, and 75% dilation recovery time. In addition, the KD test, NPC rule, and the CISS survey showed sensitivity in identifying military personnel with mTBI. Comprehensive data analysis will be performed once data collection has been completed for all 200 age-matched subjects (100 acute mTBI and 100 controls).

REFERENCES:

- Defense and Veterans Brain Injury Center (DVBIC), DoD Worldwide Numbers for TBI. 2015. <http://www.dvbic.org/dod-worldwide-numbers-tbi>.
- Marion, D.W., et al., Proceedings of the military mTBI Diagnostics Workshop, St. Pete Beach, August 2010. J Neurotrauma, 2011. 28(4): p. 517-26.
- Capó-Aponte, J.E., et al. 2013. Pupillometry as an objective biomarker for the diagnosis of blast-induced mild traumatic brain injury. Journal of Spine. Supplement Brain & Spinal Cord Injury. 2: S4-004: 1-5.

APPENDICES:

- WAMC Annual Research Symposium (6 May 2015)



Validation of Objective Visual System Biomarkers for Early Identification of Warfighters with Acute mTBI/concussion: Preliminary Results

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Co-Investigators: LTC Jose E. Capó-Aponte; MAJ David V. Walsh
Joseph Y. Dumayas



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The author(s) have no financial interest on any of the products included in this study.

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Introduction

- The DOD reported that 333,169 cases of traumatic brain injury (TBI) were confirmed since 2000, with mild TBI (mTBI) accounting for 82.4%.
- The diagnosis of mTBI has been a challenge for the military primarily because of the lack of objective assessment tools, overlap of symptoms in co-morbid conditions such as post-traumatic stress disorder (PTSD), and the interpretation of signs and symptoms by healthcare providers relies on self-reported symptoms from the injured Warfighters.
- Prompt and accurate diagnosis and management of mTBI generally increases an individual's prognosis for neurological recovery and safe return to duty (RTD).
- Premature RTD places Warfighters at greater risk of disability if they suffer an additional concussive trauma. Consequently, there is a quest for objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.



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Introduction

Gaps

- Lack of objective markers (e.g., protein, imaging, cognitive, neurosensory) to objectively diagnose Warfighters with mTBI/concussion.
- Ideal devices are: accurate, quick to perform, non-invasive, causes no discomfort or risk to patient, minimal training, deployable, low cost.
- Valid objective markers are particularly important in the field to assist deployed clinicians to make an accurate determination of fit-for-duty (FFD)/RTD or evacuation.

Objectives

- Since approximately 30 areas of the brain, and 7 of the 12 cranial nerves deal with vision, it is not unexpected that the patient with TBI may manifest a host of visual problems, such as pupillary deficit, visual processing delays, and impaired oculomotor tracking and related oculomotor-based reading dysfunctions.
- This study investigates pupillometry, version (i.e., saccades) and vergence (i.e., convergence) eye movements as potential objective biomarkers for acute mTBI.
- We have included 3 eye procedures and 1 questionnaire in this study (10 min).



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Methods

- Case-Control Correlational Design
- Approved for 200 AD military personnel aged matched
 - Preliminary data 125 subjects
 - 91 mTBI; age 19-44
 - Medically documented mTBI/concussion during the acute phase, ≤ 3 days
 - » ≤ 30 min Loss of Consciousness
 - » ≤ 24 hrs Post-Traumatic Amnesia
 - » ≤ 24 hrs Alteration of Mental State
 - » Glasgow Coma Scale score (13 – 15)
 - » Normal structural brain imaging
 - 34 Non-TBI; age 29-44



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Methods

- Pupillometry (NeurOptics PLR-200) x2
- Vergence Eye Movement (NPC ruler) x2
- Version Eye Movement (King-Devick) x2
- Convergence Insufficiency Symptom Survey



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Methods



- **Monocular** Infrared pupillometer quantifies PLR under **mesoscopic** conditions ($\sim 3 \text{ cd/m}^2$).
- The subject is asked to fixate with the non-tested eye on a distance target located at **10 feet** away.
- The pupillometer presents a **180 μW light stimulus for 185 ms**.
- It is programmed to **record PLR for 5 seconds**.
- The PLR is **recorded twice** in the right eye and then twice in the left with an interval of about **10 seconds** between the first and second recording.

NeurOptics PLR-200

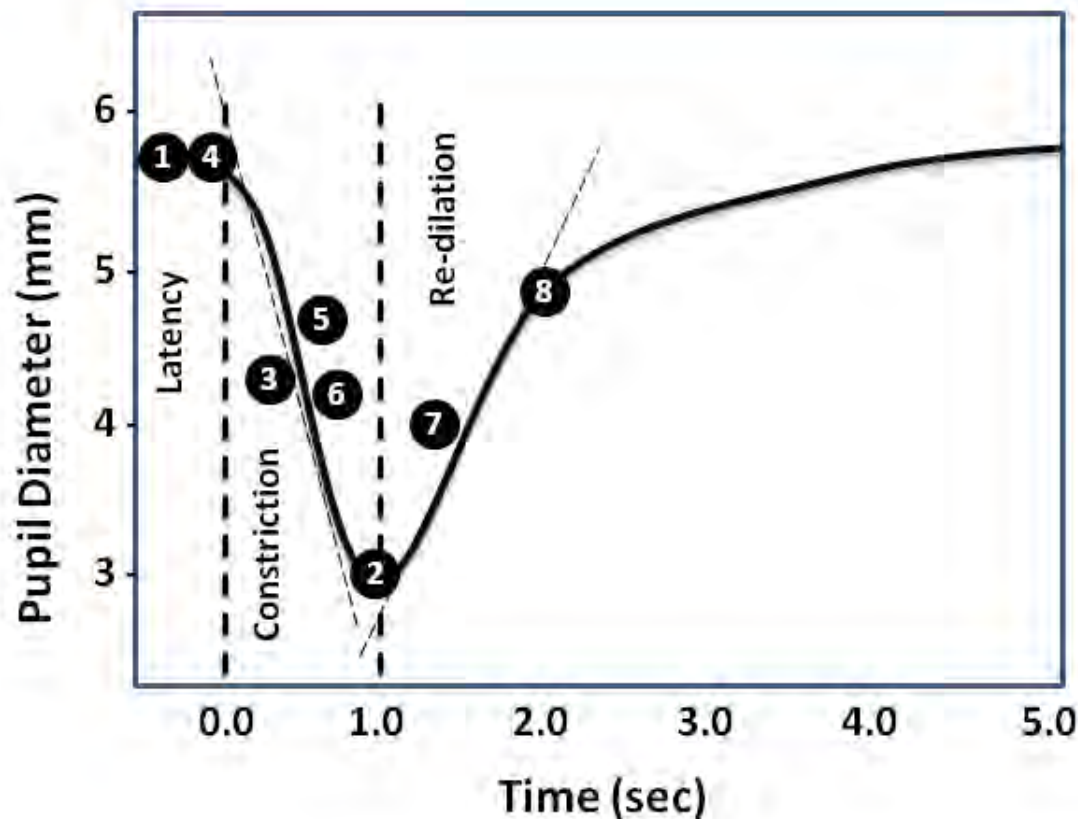
Hand-held, easy to use, quick, deployable, objective, non-invasive, requires no specialized training and causes no added discomfort or risk to the patient.



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Methods



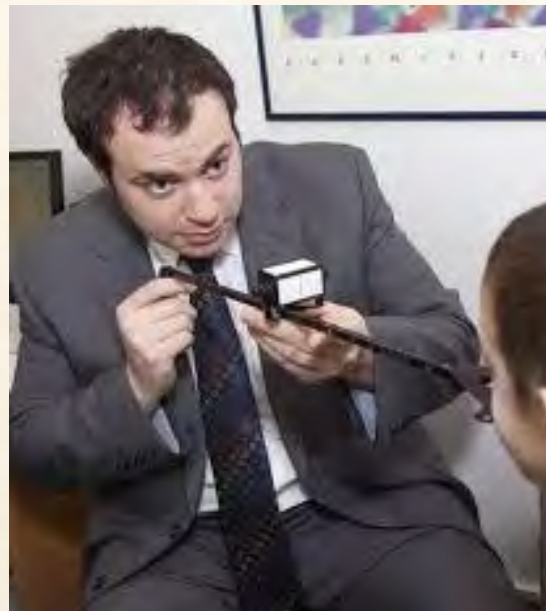
- 1) Max. Pupil Diameter
- 2) Min. Pupil Diameter
- 3) % of Constriction
- 4) Constriction Latency
- 5) Avg. Constriction Velocity
- 6) Max. Constriction Velocity
- 7) Avg. Dilation Velocity
- 8) 75% Recovery of Dilation



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Methods



R.A.F. Near Point Rule (Clement Clarke Ophth.)
20/40 Snellen single letter stimulus.



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Methods



King-Devick Test ®

- 3 test cards
- repeated twice
- mean used for analysis

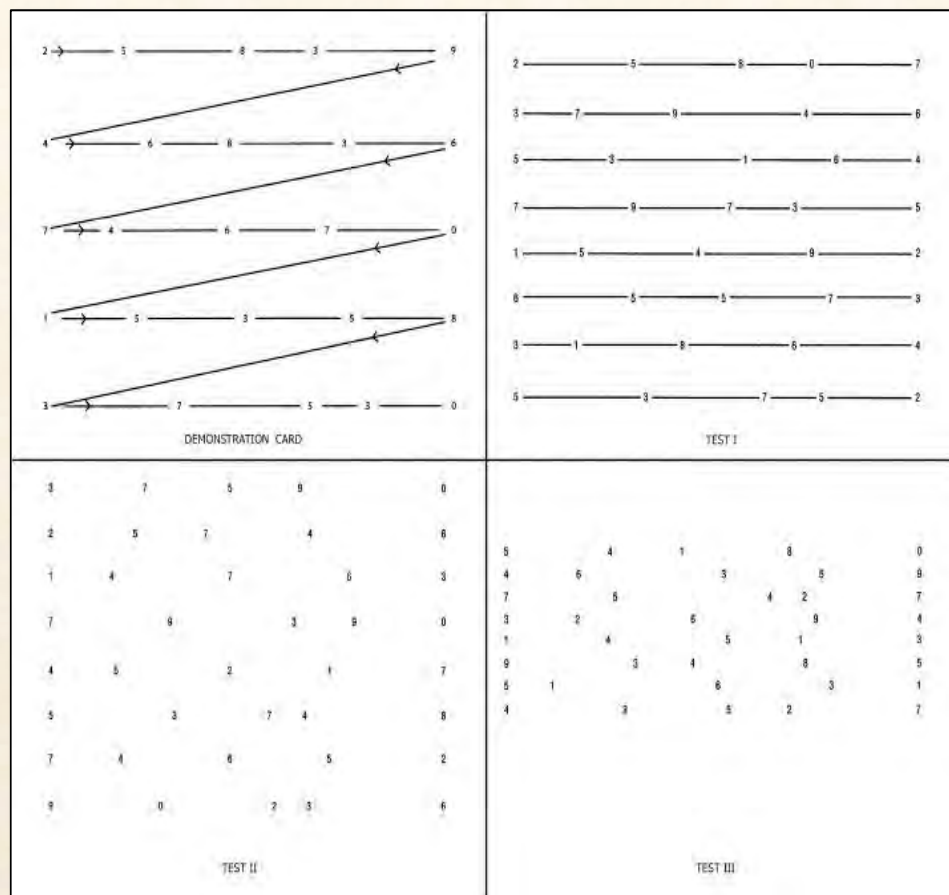


Figure A2. The King-Devick Card(s). The first card (top left) is the demonstration card, and subsequent cards are test I, II and III, respectively.





Convergence Insufficiency Symptoms Survey (CISS)

Survey Score: 0 Pass

1. Do your eyes feel tired when reading or doing close work? Never
2. Do your eyes feel uncomfortable when reading or doing close work? Never
3. Do you have headaches when reading or doing close work? Never
4. Do you feel sleepy when reading or doing close work? Never
5. Do you lose concentration when reading or doing close work? Never
6. Do you have trouble remembering what you have read? Never
7. Do you have double vision when reading or doing close work? Never
8. Do you see the words move, jump, swim or appear to float on the page when reading or doing close work? Never
9. Do you feel like you read slowly? Never
10. Do your eyes ever hurt when reading or doing close work? Never
11. Do your eyes ever feel sore when reading or doing close work? Never
12. Do you feel a 'pulling' feeling around your eyes when reading or doing close work? Never
13. Do you notice the words blurring or coming in and out of focus when reading or doing close work? Never
14. Do you lose your place while reading or doing close work? Never
15. Do you have to re-read the same line of words when reading? Never

Print Exit

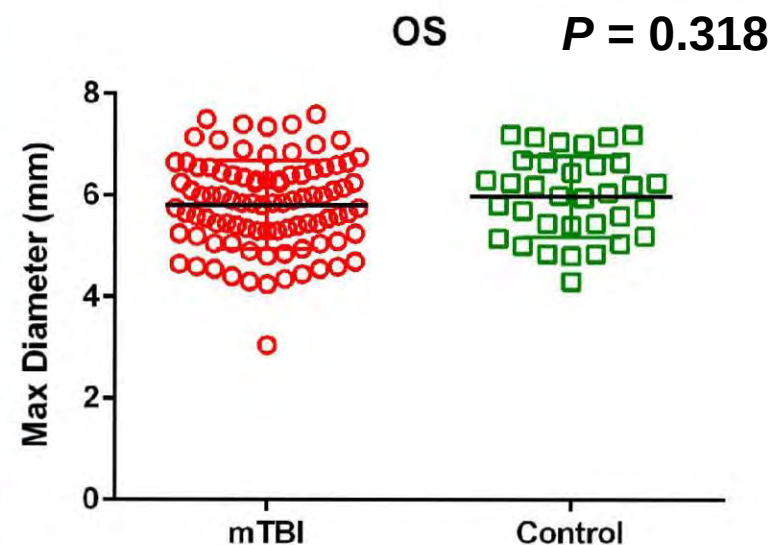
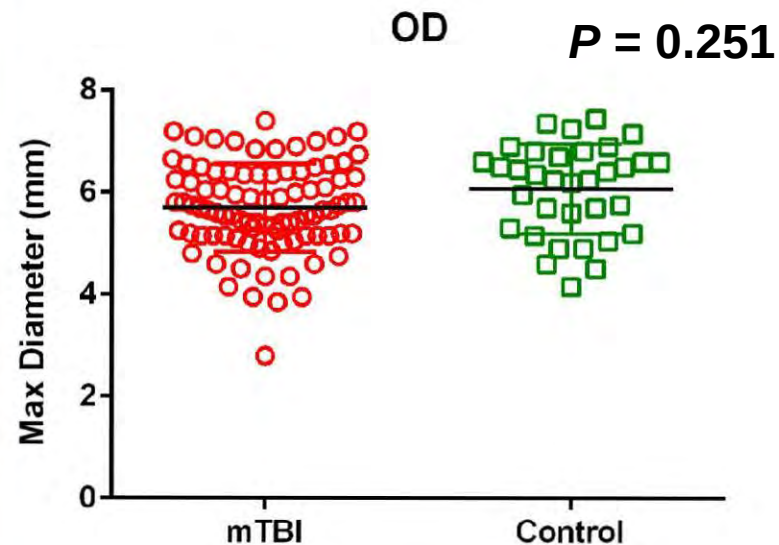
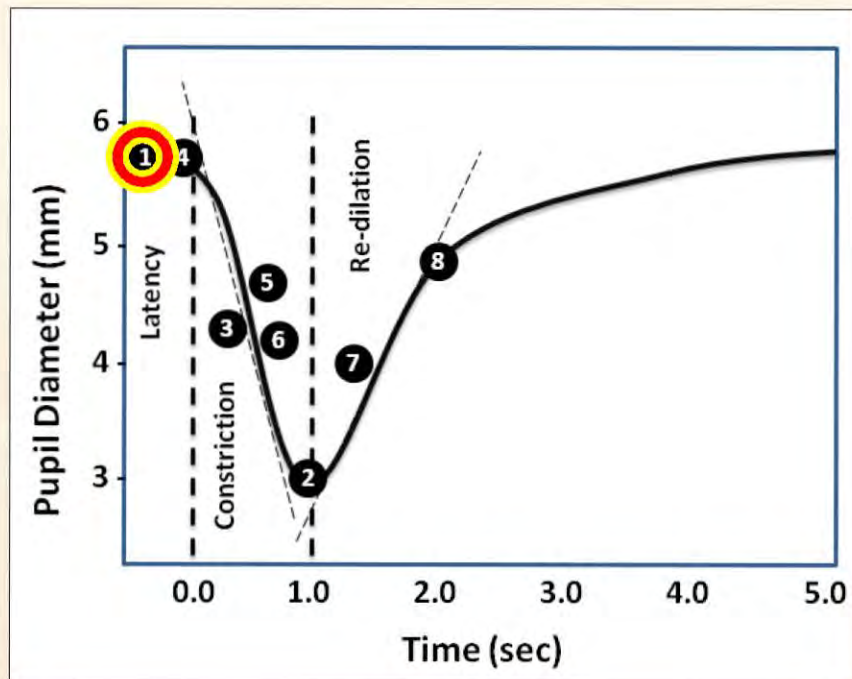
- Score:
 - always (4)
 - frequently (3)
 - sometimes (2)
 - rarely (1)
 - never (0)
- Passing score ≤ 21



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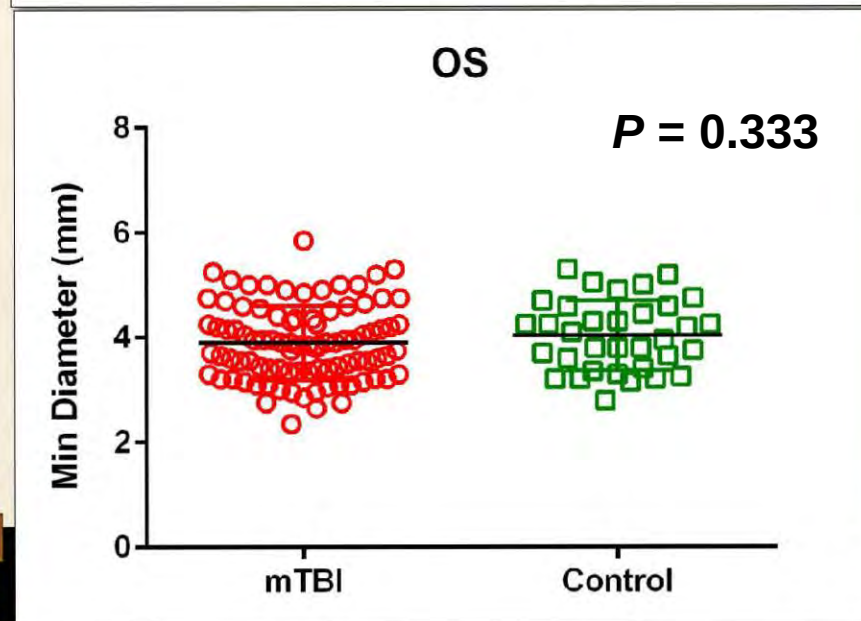
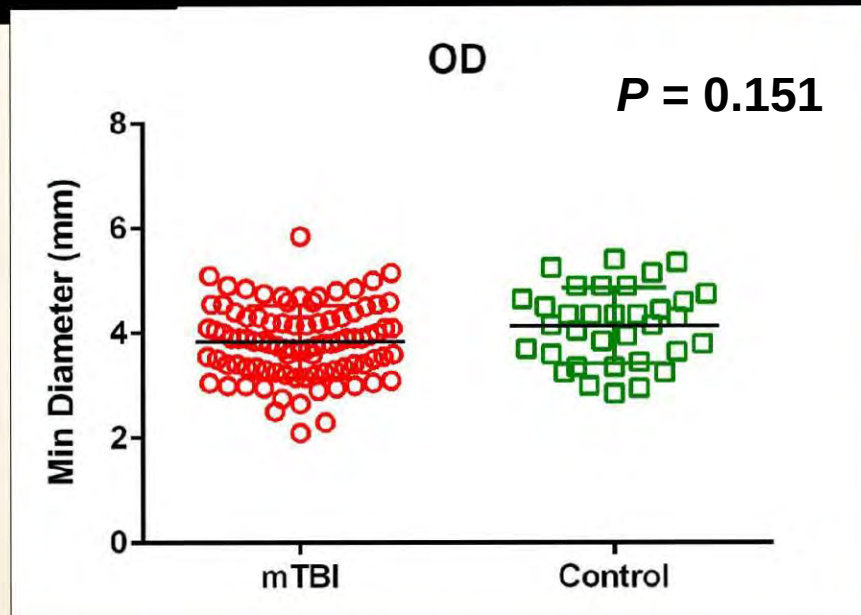
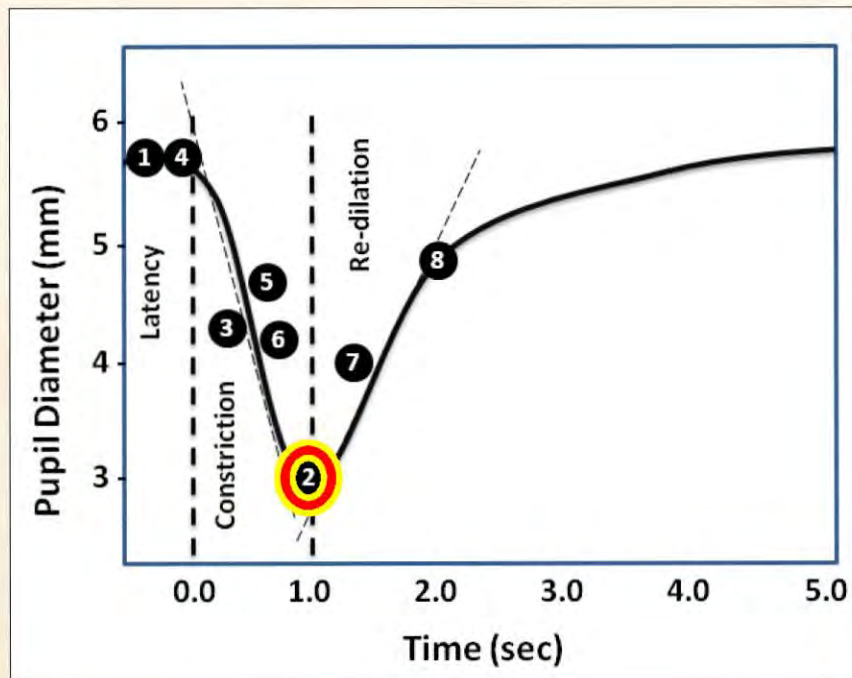


Maximum Diameter



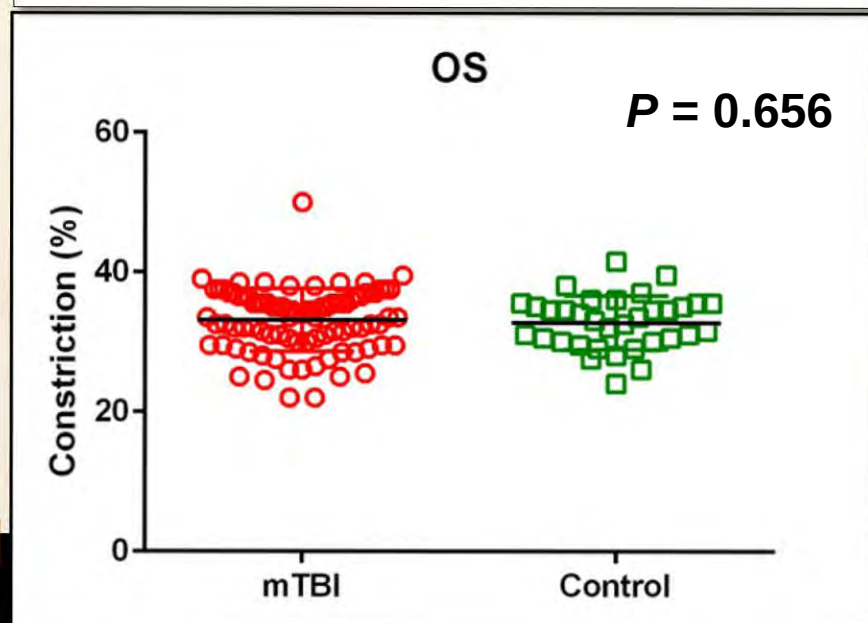
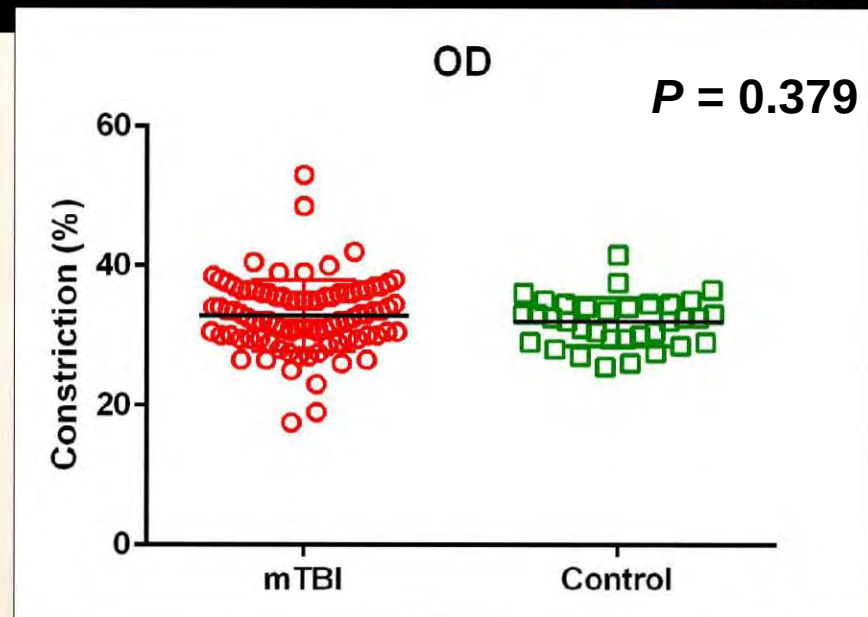
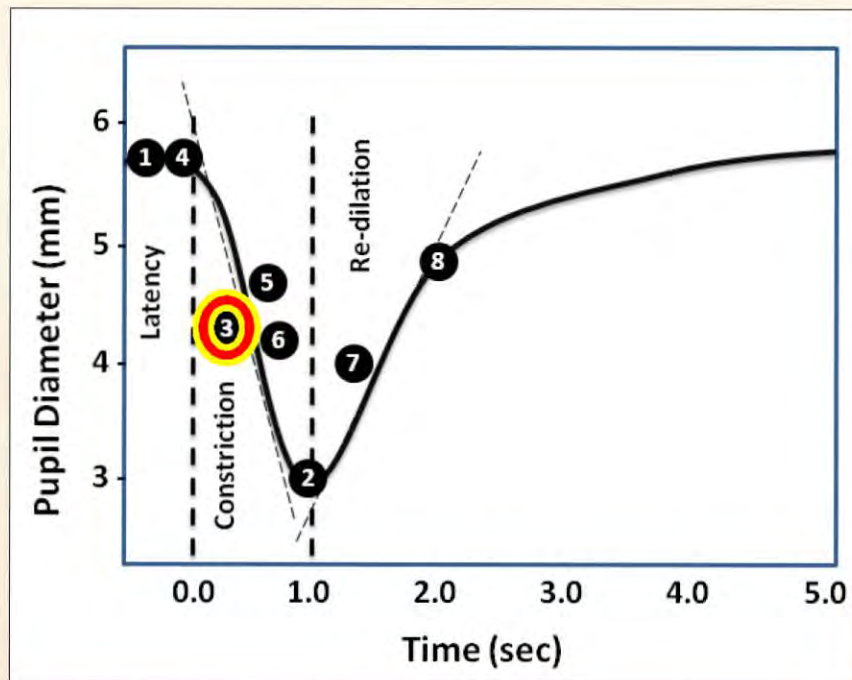


Minimum Diameter



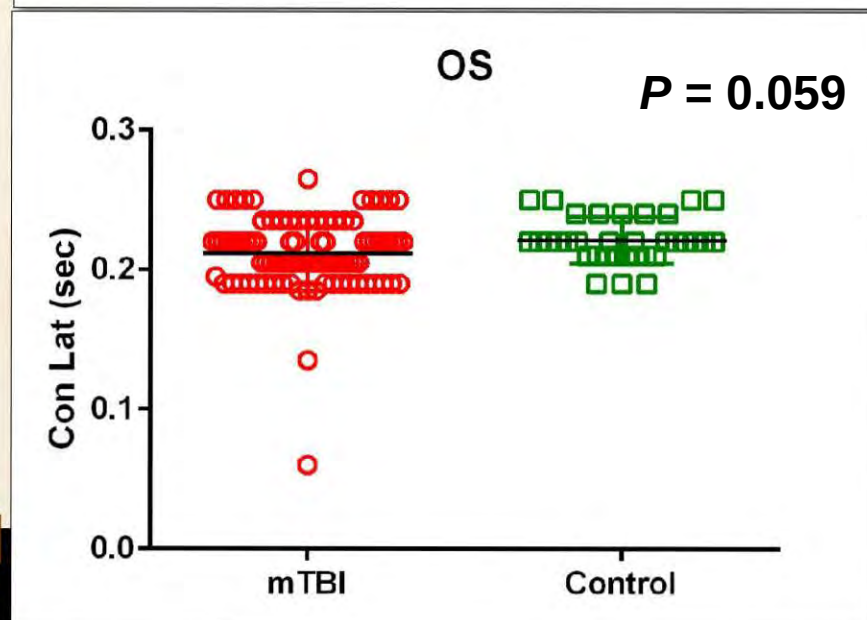
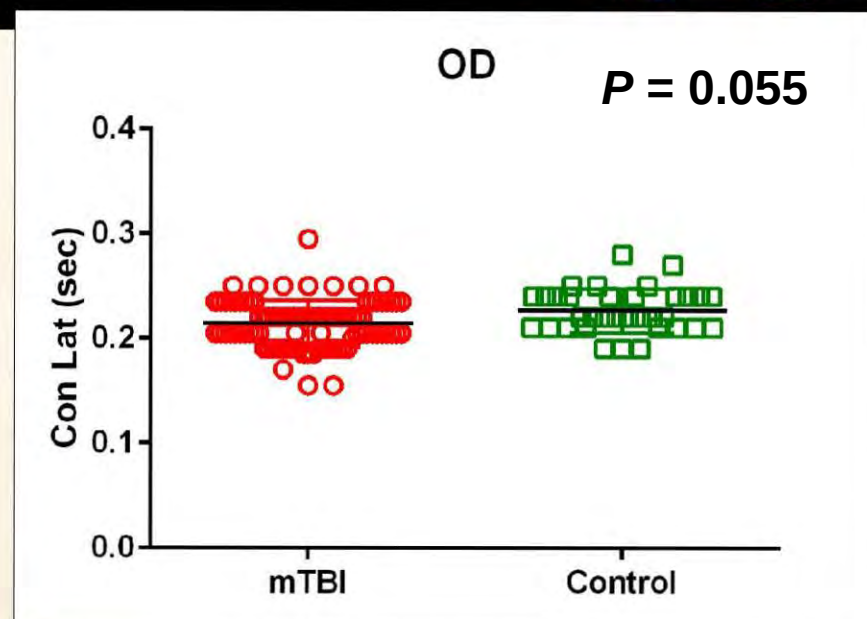
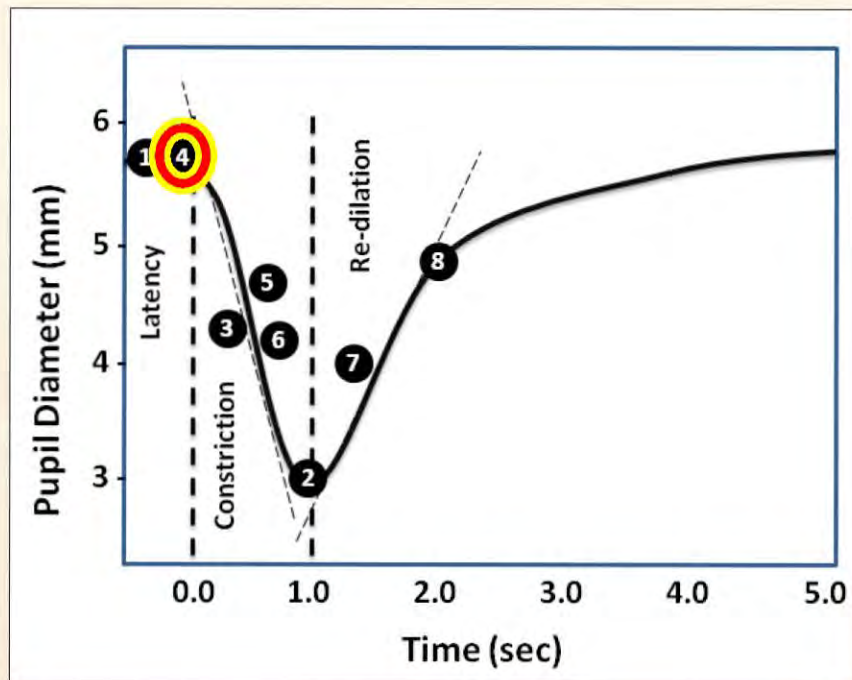


% of Constriction





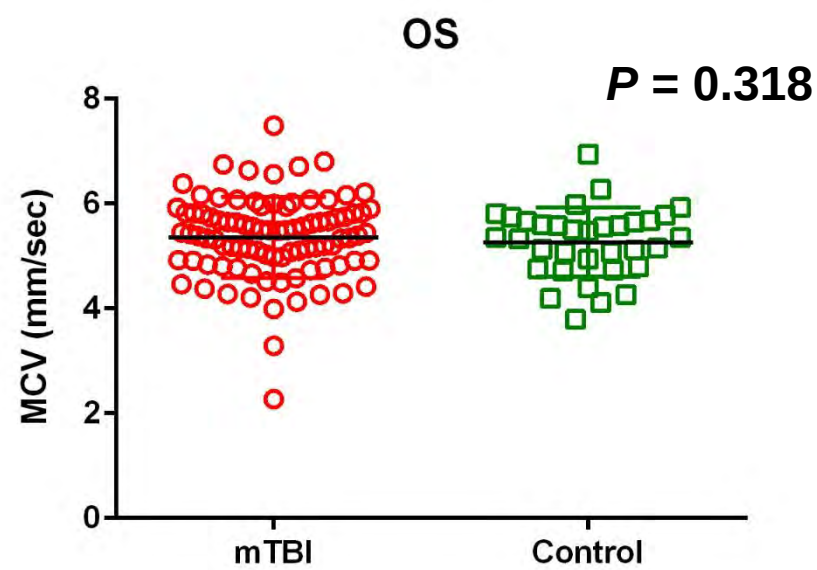
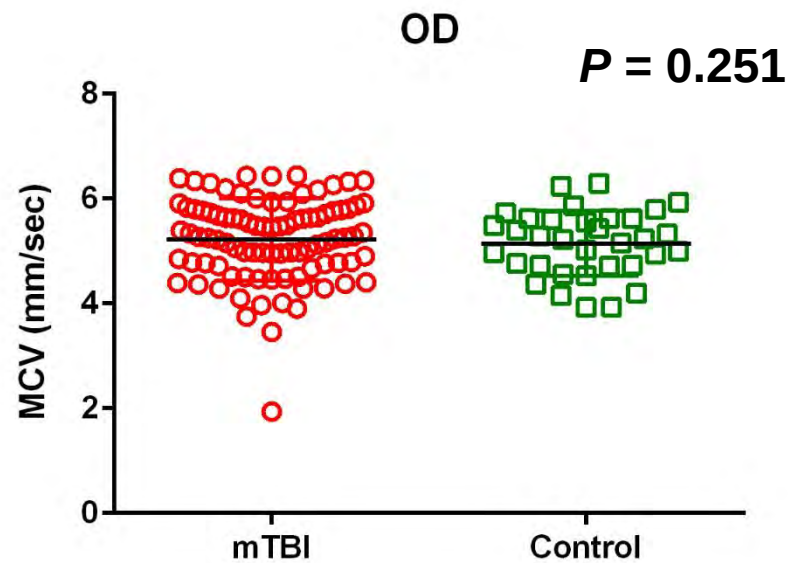
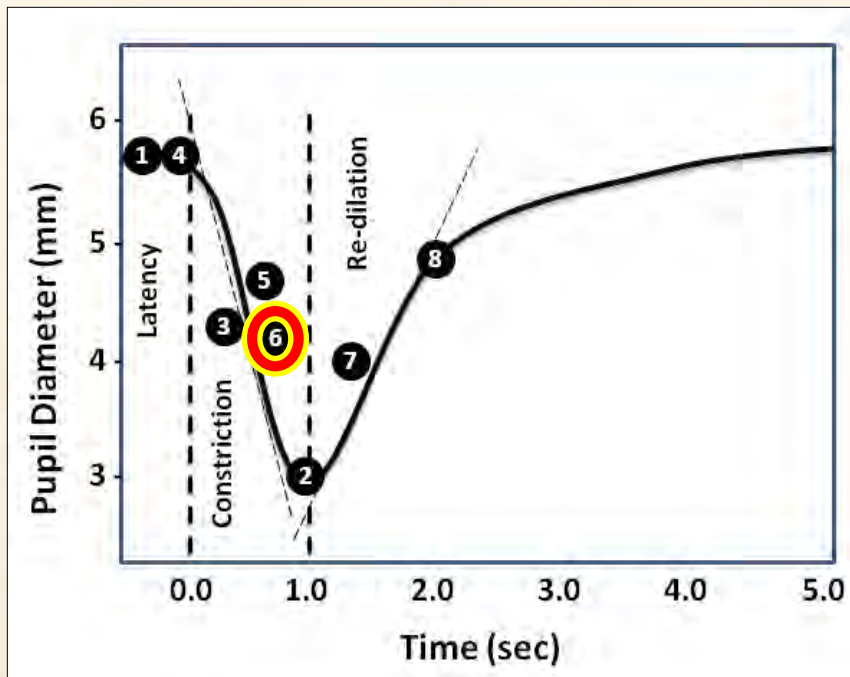
Constriction Latency



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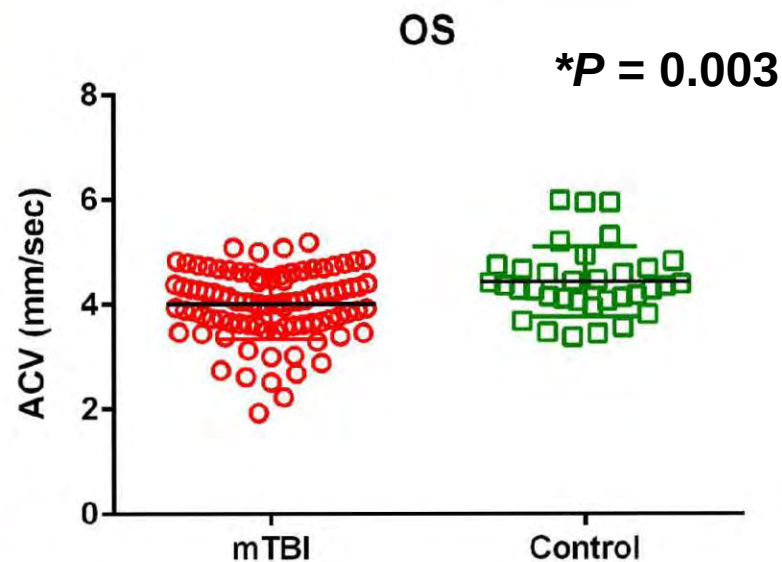
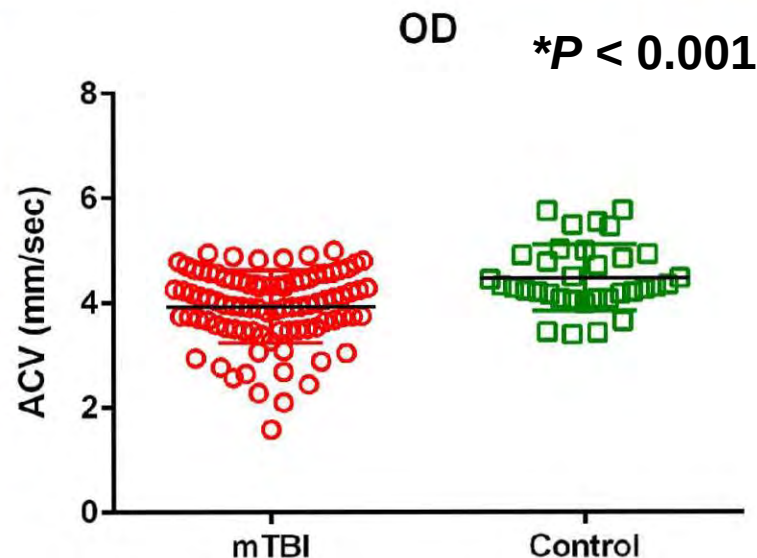
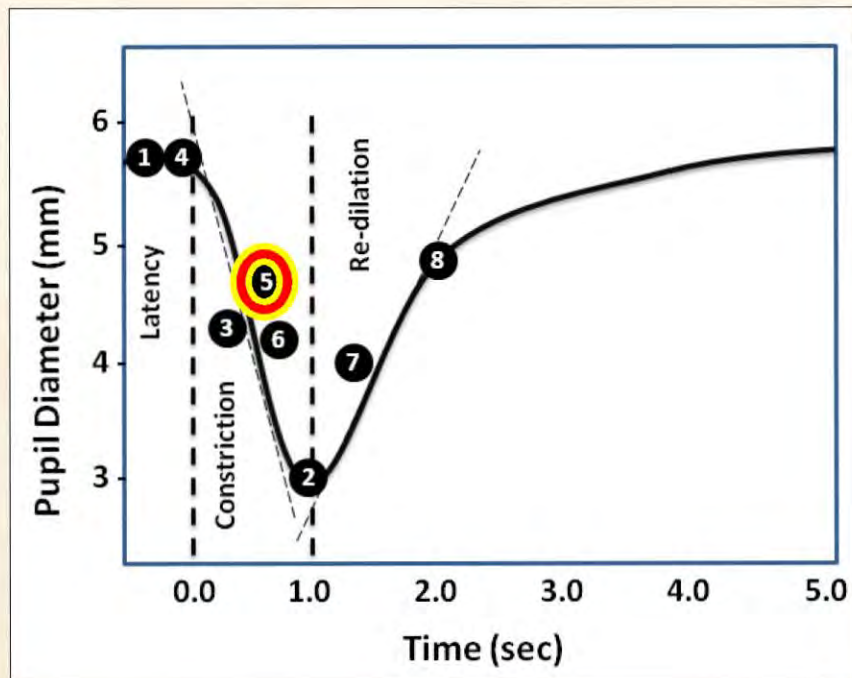
Max. Constriction Velocity



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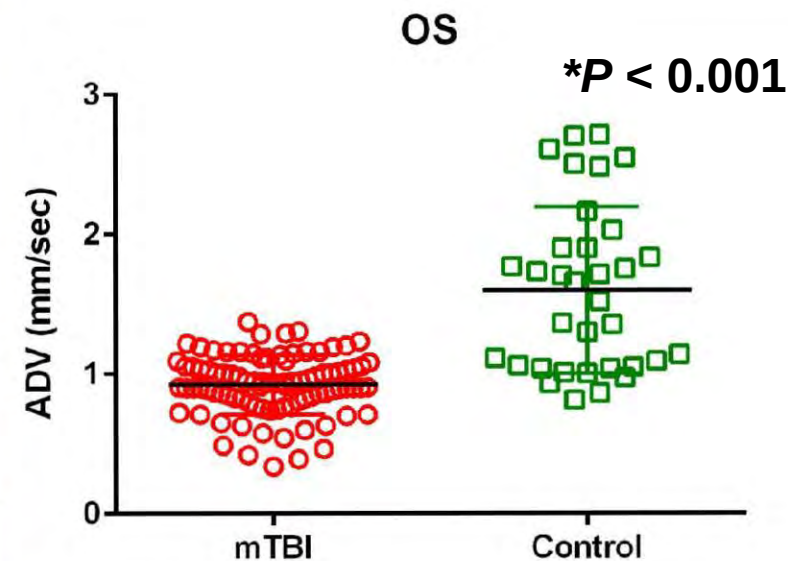
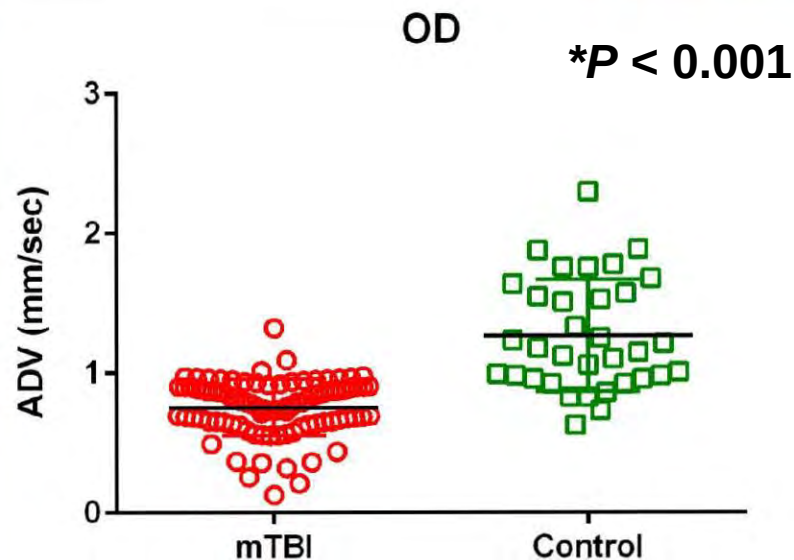
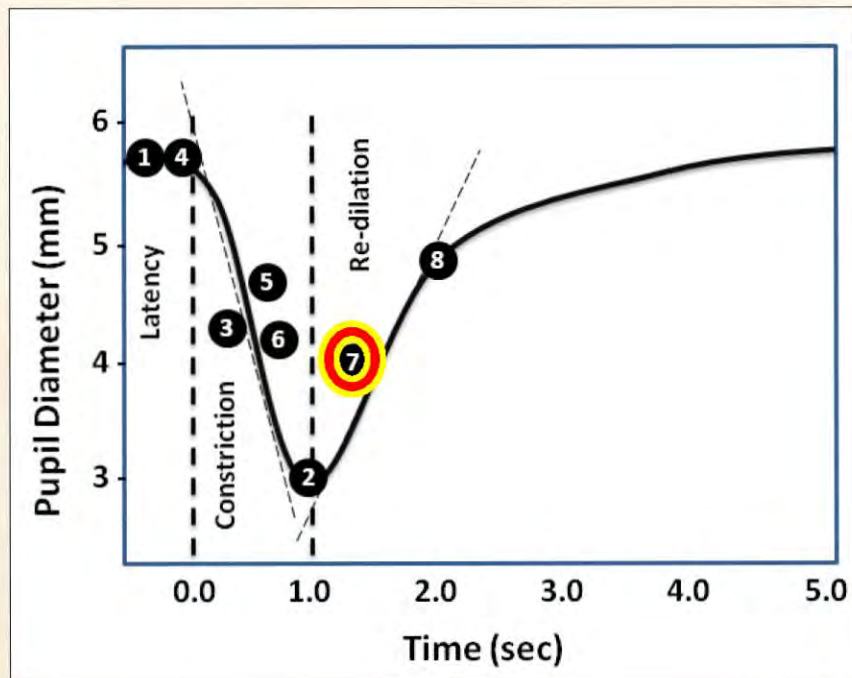


Avg. Constriction Velocity





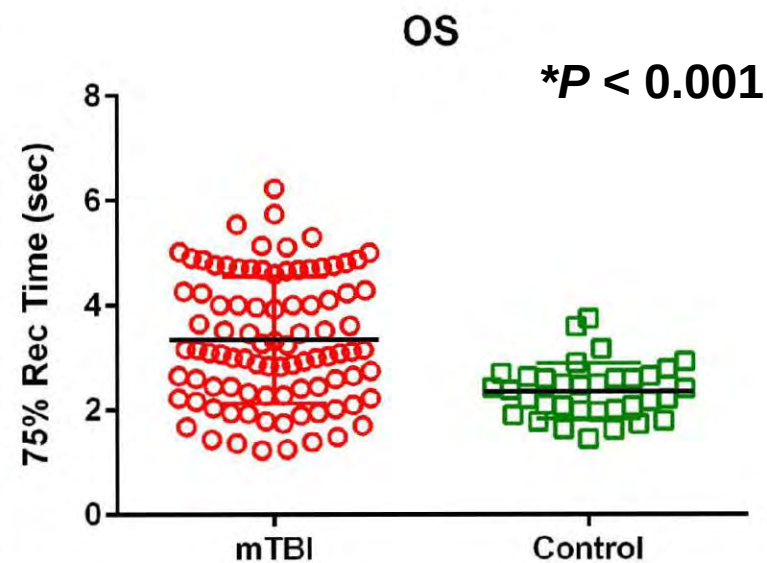
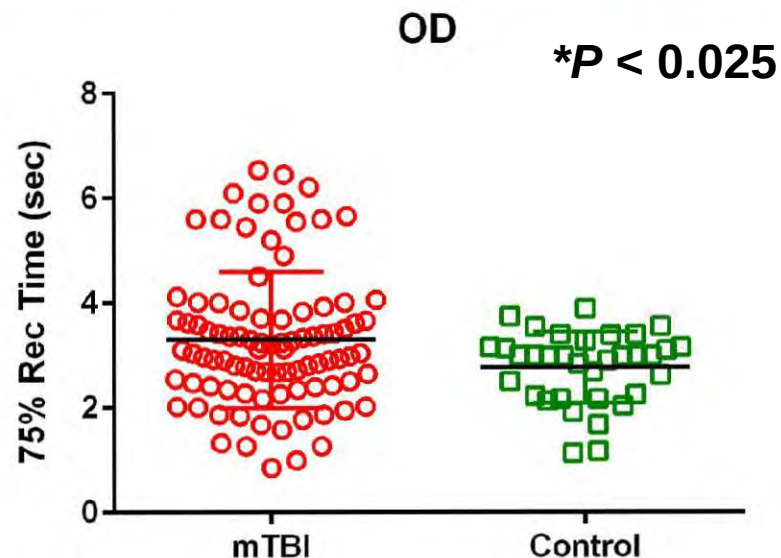
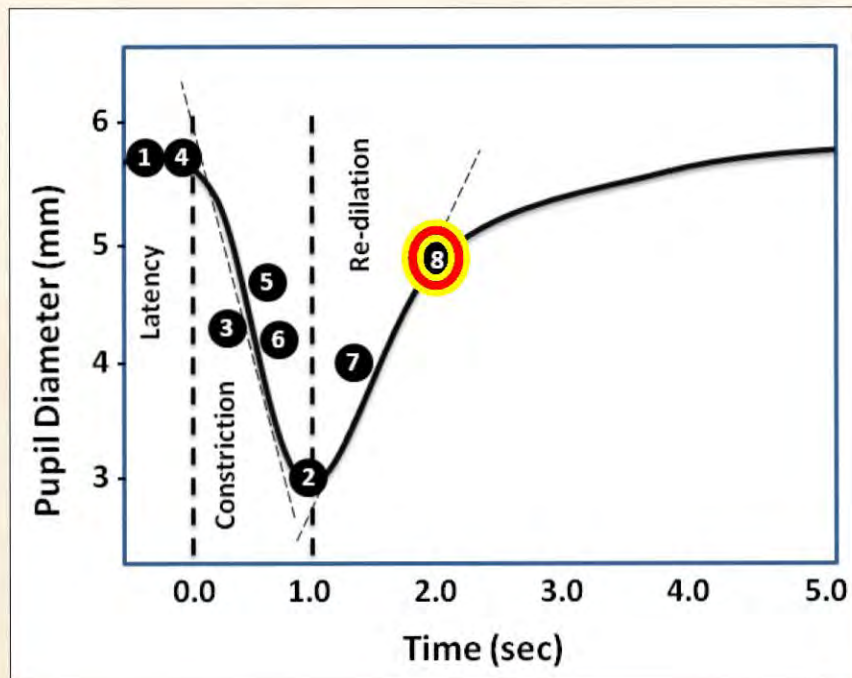
Avg. Dilation Velocity



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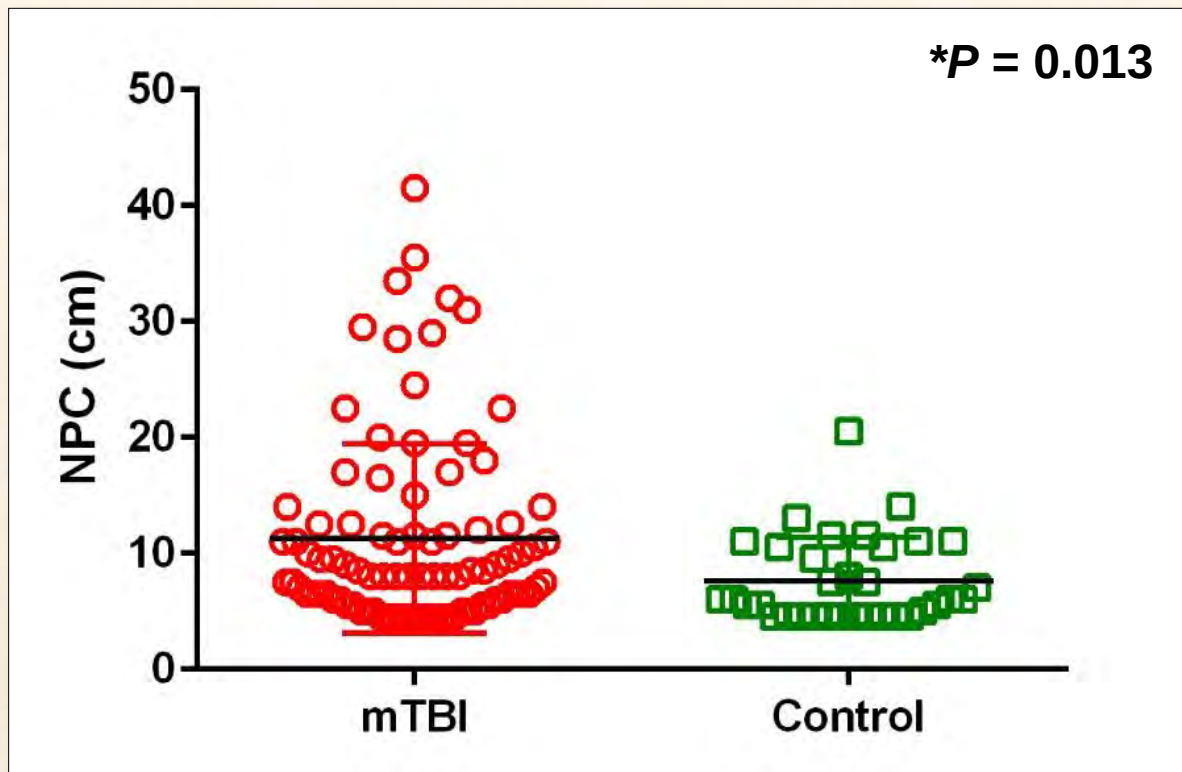


75% Recovery Time





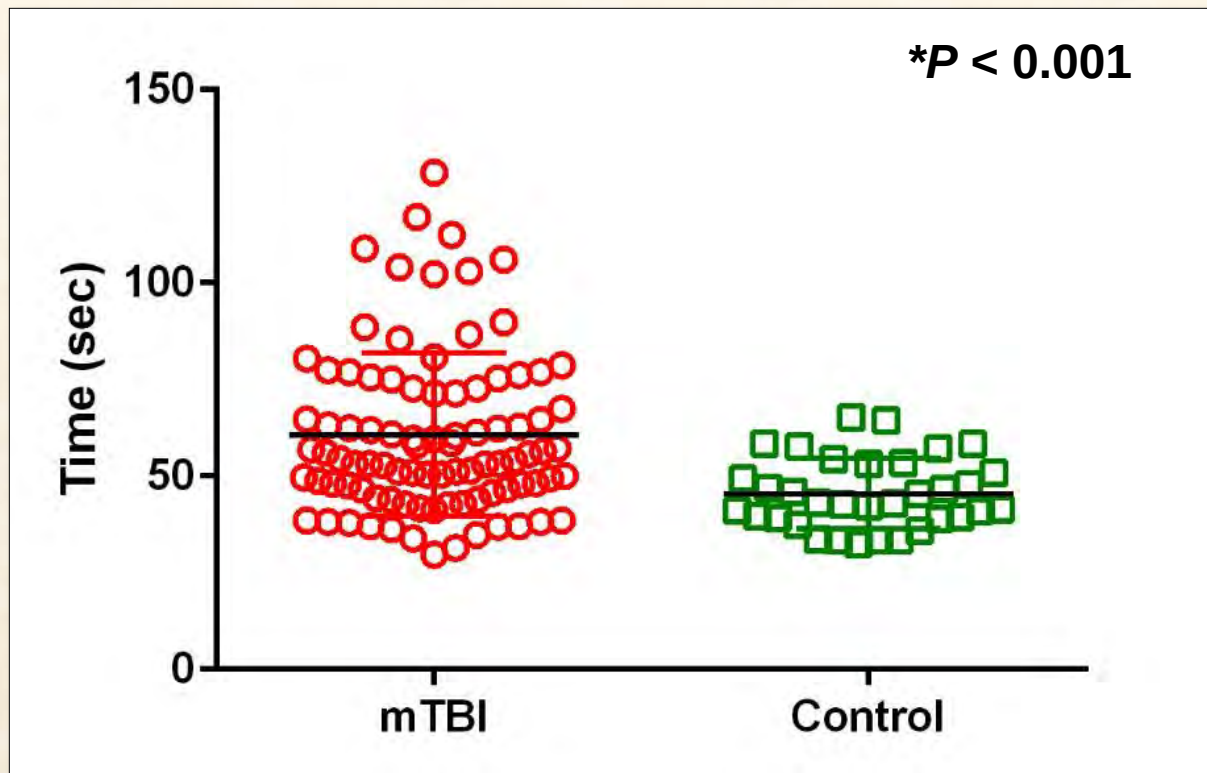
Near Point of Convergence



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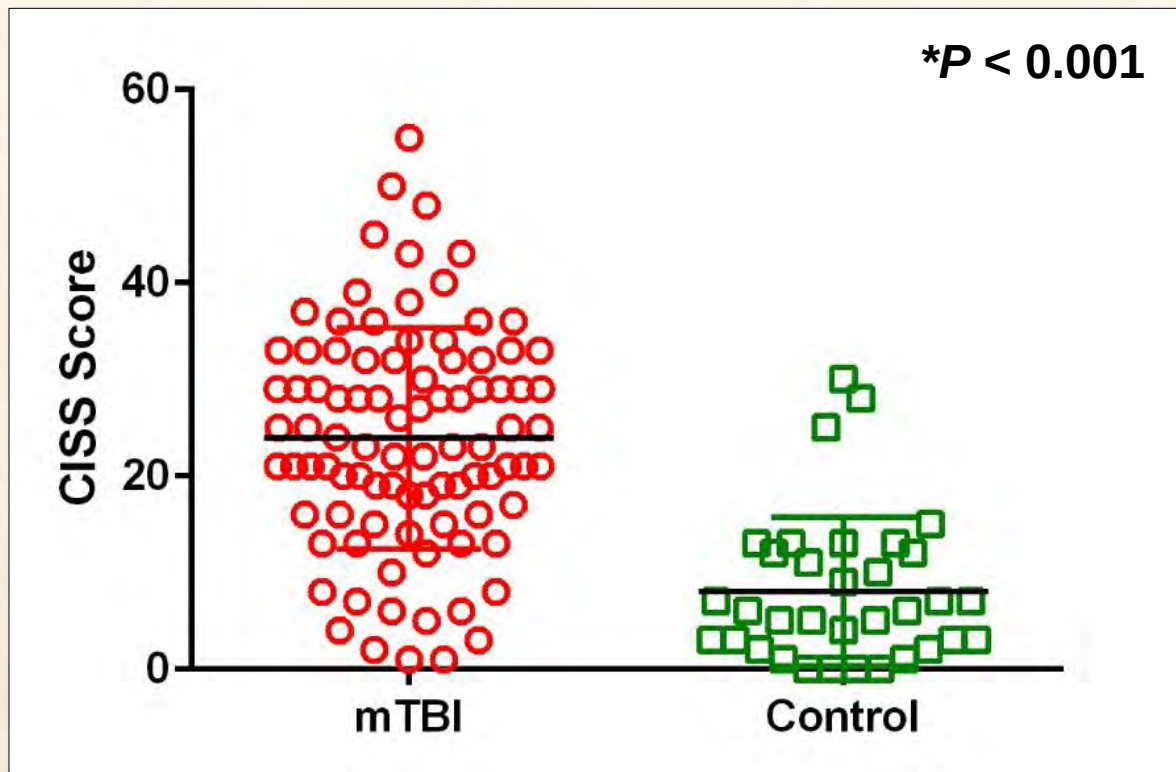
King-Devick Test



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CISS



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Discussion



- Preliminary data for all methods is proving an effective tool.
 - Objective component: PLR (i.e., ACV, ADV, T75%)
 - Objective and Subjective component: NPC
 - Subjective component: KD test
 - Good correlation with CISS
- Easily performed by subjects, including mTBI
- Easily administered by techs and doctors
- Faster (3 min) than conventional oculomotor examination (20 min)
- Provide tool to expedite mTBI diagnosis and management
- Future Direction
 - Complete data collection for aged-matched control data (non-mTBI group esp. 19-29 yo)
 - This battery of tests could be a strong candidate to determine FFD/RTD status for those Warfighter's with mTBI



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