Smartphone Pupillometry and Machine Learning for Detection of Acute Mild Traumatic Brain Injury: A Pilot Study

Anthony J Maxin, Do H Lim, Sophie Kush, Jack Carpenter, Rami Shaibani, Bernice G Gulek, Kimberly G Harmon, Alex Mariakakis, Lynn B McGrath, Michael R Levitt

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Abstract

Background: Quantitative pupillometry has been used in mTBI with changes in pupil reactivity noted after blast injury, chronic mTBI and sports-related concussion.

Objective: We evaluated the diagnostic capabilities of a smartphone-based digitial pupillometer to differentiate patients in the emergency room with mTBI from controls.

Methods: Adult patients diagnosed with acute mTBI with normal neuroimaging were evaluated in an emergency department within 36 hours of injury. Healthy adults without mTBI were enrolled as controls. The PupilScreen smartphone pupillometer was used to measure the pupillary light reflex (PLR), and quantitative curve morphological parameters of the PLR were compared between mTBI and healthy controls. To address the class imbalance present in our sample, a synthetic minority oversampling technique (SMOTE) was applied. All possible combinations of PLR parameters produced by the smartphone pupillometer were then applied as features to four binary classification machine learning algorithms: Random Forest, k-nearest neighbors, support vector machine, and logistic regression. A 10-fold cross validation technique stratified by cohort was used to produce accuracy, sensitivity, specificity, area under the curve (AUC), and F1 score metrics for the classification of mTBI versus healthy subjects.

Results: Acute mTBI patients (n=12) were 33% female, mean age 54.1 years, and 58% Caucasian with median Glasgow Coma Scale (GCS) of 15. Healthy patients (n=132) were 67% female, mean age 36 years, 64% Caucasian and median GCS of 15. Significant differences were observed in PLR recordings between healthy controls and acute mTBI patients in the following PLR parameters: Percent change (34±8.3 vs 26±7.9, $p<0.007$), minimum pupillary diameter (34.8±6.1 vs 29.7±6.1, $p<0.007$), maximum pupillary diameter (53.6±12.4 vs 40.9±11.9, $p<0.007$), and mean constriction velocity (11.5±5.0 vs 6.8±3.0, $p<0.007$) between cohorts. After SMOTE, both cohorts had a sample size of 132 recordings. The best performing binary classification model was a random forest model using latency, percent change, maximum diameter, minimum diameter, mean constriction velocity, and maximum constriction velocity PLR parameters as features. This model produced an overall accuracy of 93.5%, sensitivity of 96.2%, specificity of 90.9%, AUC of 0.936, and F1 score of 93.7% for differentiating between pupillary changes in mTBI and healthy subjects.

Conclusions: Quantitative smartphone pupillometry may be a useful tool in the diagnosis of acute mTBI.

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Short Title: Pilot Study: Smartphone Detection of Mild TBI

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Abstract

Background

Quantitative pupillometry has been used in mild traumatic brain injury (mTBI) with changes in pupil reactivity noted after blast injury, chronic mTBI and sports-related concussion.

Objectives

We evaluated the diagnostic capabilities of a smartphone-based digital pupillometer to differentiate patients in the emergency room with mTBI from controls.

Methods

Adult patients diagnosed with acute mTBI with normal neuroimaging were evaluated in an emergency department within 36 hours of injury. Healthy adults without mTBI were enrolled as controls. The PupilScreen smartphone pupillometer was used to measure the pupillary light reflex (PLR), and quantitative curve morphological parameters of the PLR were compared between mTBI and healthy controls. To address the class imbalance present in our sample, a synthetic minority oversampling technique (SMOTE) was applied. All possible combinations of PLR parameters produced by the smartphone pupillometer were then applied as features to four binary classification machine learning algorithms: Random Forest, k-nearest neighbors, support vector machine, and logistic regression. A 10-fold cross validation technique stratified by cohort was used to produce accuracy, sensitivity, specificity, area under the curve (AUC), and F1 score metrics for the classification of mTBI versus healthy subjects.

Results

Acute mTBI patients (n=12) were 33% (4 out of 12) female, mean age 54.1 years, and 58% (7 out of 12) Caucasian with median Glasgow Coma Scale (GCS) of 15. Healthy patients (n=132) were 67% (88 out of 132) female, mean age 36 years, 64% (84 out of 132) Caucasian and median GCS of 15. Significant differences were observed in PLR recordings between healthy controls and acute mTBI patients in the following PLR parameters: Percent change (34±8.3% vs 26±7.9%, $p<0.001$), minimum pupillary diameter (34.8±6.1 pixels vs 29.7±6.1 pixels, $p=0.004$), maximum pupillary diameter (53.6±12.4 pixels vs 40.9±11.9 pixels, $p<0.001$), and mean constriction velocity (11.5±5.0 pixels/second vs 6.8±3.0 pixels/second, $p<0.001$) between cohorts. After SMOTE, both cohorts had a sample size of 132 recordings. The best performing binary classification model was a random forest model using latency, percent change, maximum diameter, minimum diameter, mean

constriction velocity, and maximum constriction velocity PLR parameters as features. This model produced an overall accuracy of 93.5%, sensitivity of 96.2%, specificity of 90.9%, AUC of 0.936, and F1 score of 93.7% for differentiating between pupillary changes in mTBI and healthy subjects.

Conclusions

In this pilot study, quantitative smartphone pupillometry demonstrates the potential to be a useful tool in the future diagnosis of acute mTBI.

Introduction

The pupillary light reflex (PLR) is a biomarker of neurological disease demonstrated by the reaction of the pupil to a light stimulus [1] that is commonly used in the management of moderate to severe traumatic brain injury (TBI) [2-3]. The pupil has both sympathetic and parasympathetic innervation which can be affected by mild TBI (mTBI). Traditional PLR assessment uses a manual penlight [4]; however, this method suffers from poor inter-rater reliability, is highly subjective, and is of little use outside of moderate to severe TBI [4-5]. More recently, quantitative measurement of the PLR has been used as a biomarker for mTBI wherein the pupils are reactive but abnormal in a manner that is not easily detectable to the human eye [6]. Quantitative pupillometry is typically performed in intensive care unit (ICU) or neuro ICU settings with FDA-approved equipment (NeurOptics, Irvine, CA). There has been recent interest in the use of this same equipment in the field for the diagnosis of concussion in military personnel after blast-injury [7], to document pupillary changes in those with chronic mTBI [8-9], and most recently interest in the diagnosis of sport-related concussion [10].

We developed a smartphone quantitative pupillometry application (PupilScreen) which measures the PLR with greater accuracy and higher interrater reliability than the manual penlight

[11]. The aim of this study is to investigate the ability of the smartphone pupillometry application to differentiate between acute mTBI subjects (< 36 hours after injury) and healthy controls.

Methods

Recruitment

We used a previously developed a binocular smartphone pupillometer (PupilScreen, Apertur, Inc., Seattle, WA), which quantifies PLR curve morphological parameters (Table 1) to examine differences in pupillary reactivity between subjects with acute mTBI and healthy subjects. The smartphone pupillometry application requires a standard iPhone camera without external hardware and is connected to a cloud-based neural network computer vision algorithm [11-15]. The application interface includes an augmented reality screen overlay with eye holes that helps to standardize the distance from the phone to the pupils for each measurement [13]. Using this technique in previous studies, the median error of pupil detection to the ground truth pupil diameter in millimeters was 0.23 and the mean absolute relative percent difference between sequential measurements was 5.8±3% [12].

Table 1 – Definitions of Pupillary Light Reflex Parameters

PLR Parameters	**Description**
Latency (s)	Time from onset of light stimulus to initial pupillary constriction
Percent Change (%)	Percent change in pupillary diameter from maximum to minimum
Minimum Pupillary Diameter (px)	Minimum diameter after light stimulus
Maximum Pupillary Diameter (px)	Average resting diameter prior to light stimulus
Mean Constriction Velocity (px/s)	The average speed at which the pupil constricts after the light stimulus until the minimum diameter is reached
Maximum Constriction Velocity (px/s)	The maximum speed at which the pupil constricts after the light stimulus until the minimum diameter is reached
Mean Dilation Velocity (px/s)	The average speed at which the pupil dilates after removal of the light stimulus

px: pixels, s: seconds

This study was approved by the University of Washington Institutional Review Board (IRB #8009), and an informed consent process was followed for all subjects as approved by the IRB. Patients with a clinical diagnosis of acute mTBI were enrolled prospectively via availability sampling (as this was an exploratory pilot study) in an emergency department after presenting with head trauma and known mechanism of injury less than 36 hours post-injury from July 2022 until March 2023. Mild TBI was defined according to the American College of Rehabilitation Medicine (ACRM) criteria [16]. Subjects were excluded if they had any intracranial abnormalities on neuroimaging. A separate cohort of healthy subjects was enrolled from among hospital staff using availability sampling over the same time period, which excluded those with self-reported known neurological disease or recent history of TBI.

Statistical Analysis

The PLR parameters were averaged for each subject between the left and right eyes prior to analysis. Differences in PLR parameters between cohorts were examined using a one-tailed t-test for independent means. A P value of <.05 was considered statistically significant and a post-hoc Bonferroni correction was implemented to control the probability of committing a type I error in the results. In addition, an analysis was performed to demonstrate the classification ability of the PLR parameters as feature inputs to machine learning models in the task of differentiating between the healthy and mTBI cohorts. Due to the significant class imbalance present, a synthetic minority oversampling technique (SMOTE) [17] was used to oversample the mTBI cohort PLR parameters to match the sample size of the healthy cohort. All PLR parameters were analyzed using four separate binary classification machine learning models: Random Forest (RF), K-Nearest Neighbors (KNN), Logistic Regression (LR), and Support Vector Machine (SVM) [18]. 10-fold cross validation stratified by cohort (which respects the independence of the training and testing sets) was used to produce the following model performance metrics on the unseen test datasets: Overall accuracy, sensitivity, specificity, area under the curve (AUC), and F1 score. We report the best-performing feature combinations for each model type, based on AUC value, in differentiating PLR curves of patients with mTBI from healthy controls.

Results

Cohort Characteristics

A total of n=12 patients diagnosed with mTBI and n=132 healthy subjects were enrolled. Subject demographics are listed in Table 2 and characteristics of their injury are listed in Multimedia Appendix 1. Acute mTBI subjects were studied on average 6.8 hours (range: 0.5-29 hours) after injury. Ten out of twelve in this sample had loss of consciousness (LOC) (< 30 min) and ten out of twelve had post-traumatic amnesia (PTA). Mechanism of injury included motor vehicle collisions (n=2), motorcycle collisions (n=2), falls (n=6), and assaults (n=2).

Table 2 – Demographic Characteristics

	Healthy	mTBI
Mean Age (SD)	36 (10.2)	54.1 (22.3)
Female (%)	67 (88 out of 132)	33 (4 out of 12)
White (%)	64 (84 out of 132)	58 (7 out of 12)
Asian (%)	18 (24 out of 132)	8 (1 out of 12)
Black (%)	9 (12 out of 132)	17 (2 out of 12)
Hispanic (%)	6 (8 out of 132)	17 (2 out of 12)
Other (%)	3 (4 out of 132)	0 (0 out of 12)
Median GCS	15	15[a]

SD: standard deviation; [a]One subject had GCS of 14

Statistical Analysis Results

Sample healthy and mTBI PLR curves produced by the smartphone application are shown in Multimedia Appendix 2. Significant differences were observed in PLR parameters of minimum diameter (p=0.004), percent change, maximum diameter, and mean constriction velocity (p<0.001) (Table 3).

Table 3 – Smartphone Pupillometry PLR Parameters in Healthy and mTBI Subjects

PLR Parameter	Healthy Mean (SD)	Acute mTBI Mean (SD)	*P* value
Latency (s)	0.21 (0.075)	0.19 (0.12)	.17
Percent Change (%)	34 (8.3)	26 (7.9)	**<.001**
Minimum Pupillary	34.8 (6.1)	29.7 (6.1)	**.004**

Diameter (px)			
Maximum Pupillary Diameter (px)	53.6 (12.4)	40.9 (11.9)	**<.001**
Mean Constriction Velocity (px/s)	11.5 (5.0)	6.8 (3.0)	**<.001**
Max Constriction Velocity (px/s)	48.9 (20.5)	38.7 (28.8)	.057
Mean Dilation Velocity (px/s)	5.4 (2.3)	3.9 (2.1)	.015

SD: Standard Deviation, px: pixels, s: seconds

In the binary classification analysis, the SMOTE [17] produced a sample size of n=132 mTBI PLR recordings and n=132 healthy PLR recordings. The best performing feature combinations based on AUC value across the four model types are listed in Table 4. The best performing model overall was RF, with the latency, percent change, minimum diameter, maximum diameter, mean constriction velocity, and maximum constriction velocity PLR parameters used as features. After stratified 10-fold cross validation, this model produced an overall accuracy of 93.5%, sensitivity of 96.2%, specificity of 90.9%, AUC of 0.936, and F1 score of 93.7% for differentiating between PLR curves of mTBI and healthy cohort.

Table 4 – Best Performing Binary Classification Models

Model	PLR Parameter Combination	Accuracy %	Sensitivity %	Specificity %	AUC	F1 Score %
RF	Latency, percent change, maximum diameter, minimum diameter, mean constriction velocity, maximum constriction velocity	93.5	96.2	90.9	0.936	93.7
KNN	Percent change, maximum	91.7	94.7	88.8	0.918	91.9

	diameter, minimum diameter					
SVM	Percent change, minimum diameter, mean constriction velocity, mean dilation velocity	86	91	81	0.86	86.7
LR	Maximum diameter, mean constriction velocity, mean dilation velocity	86.3	95.5	77.4	0.864	87.7

AUC: Area Under the Curve, RF: Random Forest, KNN: K-Nearest Neighbors, SVM: Support Vector Machine, LR: Logistic Regression

Discussion

Principal Results

We present data comparing PLR parameters (Table 1) in a cohort of acute mTBI patients compared with healthy controls. Our results indicate that statistically significant differences can be detected between the mean PLR parameters of patients with acute mTBI and healthy controls using smartphone quantitative pupillometry. The percent change, minimum diameter, maximum diameter, and mean constriction velocity PLR parameters were significantly lower in the acute mTBI cohort (Table 3). This reflects the functional rather than structural abnormalities in neuronal homeostasis that are the basis of mTBI pathophysiology [19]. After using SMOTE [17] to resolve the class imbalance in our sample, we observed the performance of four binary classification models for differentiating between acute mTBI and healthy controls (Table 4), the best of which produced accuracy, sensitivity, specificity, AUC, and F1 score all above 90%, suggesting useful diagnostic discrimination.

Comparison with Prior Work

There has been increased interest in PLR as a physiologic biomarker of mTBI and in automated pupillometry. One study of the NPi-200 commercial pupillometry device in blast-induced mTBI patients 15-45 days post-injury found that mean constriction velocity, latency, and mean dilation velocity were slower than controls [7]. A follow-up study of 100 concussed soldiers compared to 100 non-concussed controls < 72 hours post-injury had similar findings [20]. Pupillary changes have also been demonstrated in those with chronic mTBI compared to controls > 45 days and > 1 year post injury using automated quantitative pupillometry [8-9]. Most recently changes in pupillary reactivity were demonstrated in 98 concussed youths compared to 134 controls at a median of 12 days post-injury [10]. Smartphone applications have also been studied previously in the diagnosis and management of concussion and mTBI based on subjective clinical findings [21-23], though prior to the present study only one has used pupillometry [24].

Detailed Discussion of Current Work

The smartphone pupillometer used in the current study (PupilScreen) has several advantages over more traditional devices. It is more affordable and would be more accessible and practical in clinical care settings outside of the hospital. It also has demonstrated improved performance when compared to a proprietary pupillary reactivity index [25] in the setting of severe TBI [14], without effects from opioid medication use [15]. The smartphone pupillometer in this study has also shown potential utility in the diagnosis of other neurological conditions such as in the detection of acute pre-intervention ischemic stroke while a proprietary pupil index [25] remained within the normal and reactive range for all stroke subjects [13]. Other quantitative pupillometry technologies have been studied with varying hardware and software features and requirements [25-29], yet these technologies have not been studied as extensively, do not support simultaneous binocular recording of the PLR for dynamic assessment, and do not incorporate machine learning to uncover nuanced relationships between PLR parameters that may not be easily summarized in a proprietary reactivity index [25].

In this study, we observed alterations of the autonomic nervous system in mTBI compared to healthy controls (reduction in maximum and minimum pupil diameters) and direct effects of mTBI functional pathophysiology on cranial nerve III or its post-ganglionic short ciliary nerve derivatives [1] (difference in percent change and mean constriction velocity parameters). These results correlate with previous studies in acute mTBI [20] on the importance of the mean constriction velocity but not on that of the mean dilation velocity, which may be due to mechanical differences in the method of capture between other quantitative pupillometers and the smartphone quantitative pupillometer used in this study. A report of patients with chronic mTBI demonstrated findings similar to our study (despite evaluating chronic, rather than acute mTBI), finding significant differences seen in the maximum resting pupillary diameter, mean constriction velocity, maximum constriction velocity, mean dilation velocity, and percent change PLR parameters [8]. Our study is unique in that it includes only subjects within 36 hours after injury, unlike others for which recruitment occurred up to several weeks after mTBI [7-10] and in that it uses smartphone pupillometry as an accessible and practical alternative to traditional quantitative pupillometry.

Using Multimedia Appendix 2 as an example, PLR curves between a healthy control and an acute mTBI patient look subjectively similar to the naked eye. Despite this, a statistically significant difference was found in the structural curve morphology parameters listed above, indicating that using these quantitative PLR parameters in combination (rather than each one alone) may be necessary to detect subtle changes that may be present in acute mTBI. The results of our binary classification models support this, as when the PLR parameters are used in combination with one another as features in a machine learning binary classification model, we see a reasonable capability of the model of differentiate between healthy and acute mTBI subjects with greater than 90% on all model performance metrics. In addition, the important PLR parameters mirror those from the literature and our own individual parameter comparison results. While preliminary, our results show promise in the usage of a mobile smartphone pupillometer with advanced PLR analysis to detect mTBI, which could have major implications in fields such as athletics, prehospital care, the military, and digital health in general. Although we did not evaluate the diagnostic spectrum of mild, moderate, and severe TBI in this pilot study, such work is ongoing using the smartphone pupillometer studied here. In addition, we believe that there is value in studying an objective tool for acute mTBI differentiation from healthy controls as it has been demonstrated in the literature that cases of acute mTBI are missed in the acute care setting (such as the emergency department setting wherein the present study was conducted) [30-31].

Limitations

This study is limited by multiple factors; the small sample size of n=12 acute mTBI patients. We have addressed this limitation via our use of SMOTE [17] to equalize the sample size of both cohorts to 132 recordings for binary classification machine learning analysis, nonetheless, larger studies are required for external validation and there is a risk of overfitting in the machine learning models when using this approach. Another limitation of this approach is the possibility that the sample of patients with acute mTBI is not representative of the broader acute mTBI population. Using the case descriptions in Multimedia Appendix 1, a heterogeneous distribution of case types is seen with a wide range in time after injury, variety of mechanisms (falls, assaults, motor vehicle collisions), and findings on examination that are qualifying for the ACRM definition of acute mTBI. Thus, we believe that despite the small sample size, we have captured a somewhat representative group of the broader emergency department population with acute mTBI using availability sampling. Other limitations are the mechanism of injury, which was entirely mechanically induced, which may limit the application of our findings to blast-induced injury subjects in military settings [7]. Finally, our healthy cohort was younger than the acute mTBI cohort, and thus known changes in the PLR along the spectrum of aging [32] may have affected our results.

Conclusions

In this pilot study, mobile pupillometry using a smartphone app detected significant differences in PLR parameters and performed with greater than 90% accuracy, sensitivity, specificity, AUC, and F1 score on binary classification between acute mTBI and healthy cohort. The technology studied in this pilot study may have potential future use in hospital or non-hospital settings to detect acute mTBI and concussion after future validation to test its generalizability and stability of its predictions on prospectively collected external testing datasets.

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None.

Conflicts of Interest

MRL: Consultant for Apertur, Medtronic, Aeaean Advisers, Metis Innovative, Stereotaxis; Equity interest in Apertur, Proprio, Stroke Diagnostics, Synchron, Hyperion Surgical, Fluid Biomed; Editorial board of Journal of NeuroInterventional Surgery. BGG: None. AJM: Equity interest in Apertur. LBM: Co-founder with equity interest in Apertur. DHL: None. JC: None. SK: None. RS: None. KGH: None. AM: None.

("Multimedia Appendix 1: [Table – Injury Characteristics]")

("Multimedia Appendix 2: [Figure 1 – Acute mTBI (A) and healthy subject (B) PLR Curves. Top panel: PLR curve of right (red) and left (blue) eyes. Bottom panel: Brightness of the recording as detected by the smartphone camera. Although some motion artifact is present in both curves, the mTBI and healthy subject curves appear qualitatively similar with pupillary constriction during increased brightness (due to the light stimulus from the smartphone camera flash) and pupillary re-dilation towards baseline diameter after cessation of light stimulus. Brightness is a unitless measurement of the ambient brightness detected by the built-in iPhone camera during the entire recording of the PLR. It is reported in APEX (Additive System of Photographic Exposure) which is an iPhone-specific measurement; more details can be found in iPhone software documentation.]")

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Abbreviations

PLR: pupillary light reflex

TBI: traumatic brain injury

mTBI: mild traumatic brain injury

ICU: intensive care unit

FDA: United States Food and Drug Administration

IRB: Institutional Review Board

ACRM: American College of Rehabilitation Medicine

SMOTE: synthetic minority oversampling technique

KNN: k-nearest neighbors

RF: random forest

LR: logistic regression

SVM: support vector machine

AUC: area under the curve

LOC: loss of consciousness

PTA: post-traumatic amnesia

APEX: additive system of photographic exposure

Supplementary Files

Multimedia Appendixes

Table – Injury Characteristics.
URL: http://asset.jmir.pub/assets/c81b29b54c98f90293f0fa3e66afe7d6.docx

Acute mTBI (A) and healthy subject (B) PLR Curves. Top panel: PLR curve of right (red) and left (blue) eyes. Bottom panel: Brightness of the recording as detected by the smartphone camera. Although some motion artifact is present in both curves, the mTBI and healthy subject curves appear qualitatively similar with pupillary constriction during increased brightness (due to the light stimulus from the smartphone camera flash) and pupillary re-dilation towards baseline diameter after cessation of light stimulus. Brightness is a unitless measurement of the ambient brightness detected by the built-in iPhone camera during the entire recording of the PLR. It is reported in APEX (Additive System of Photographic Exposure) which is an iPhone-specific measurement; more details can be found in iPhone software documentation.
URL: http://asset.jmir.pub/assets/0dd702639c4cd7f8d52f78443a47ee1c.png

CONSORT (or other) checklists

CONSORT EHEALTH V1.6 - with full responses.
URL: http://asset.jmir.pub/assets/ac542387ffa00a43394c39f7d7f20ecf.pdf