Article • What Pupils Remember: Exploring the Relationship between Dynamic Pupil Parameters and Self-Reported History of Mild Traumatic Brain Injury

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ABSTRACT

Background: Whether a history of mild traumatic brain injury (mTBI) affects pupil dynamics that could confound the interpretation of pupil data in other causes of visual dysfunction is unknown. We investigated the relationship between history of mTBI and pupil dynamics recorded with high-definition pupillography.

Methods: Subjects (n = 137) aged 19 to 81 years were enrolled from attendees of an optometric meeting in 2016. The data collected included: ocular and systemic health histories, current medications, history of TBI, and pupil dynamics using the automated afferent pupillary defect protocol of the RAPDx (Konan Medical). Multiple regressions with backward analysis were used to identify factors that predicted pupil dynamics.

Results: Thirty-five subjects reported positive history of mTBI (15 reported more than 1 mTBI). None of the pupil parameters assessed for either eye were predicted by history of mTBI. Time from most recent head injury to pupil testing predicted only latency of constriction onset of each eye (right eye: P = 0.02, R2 = 0.214; left eye: P = 0.02, R2 = 0.187). Age and time from most recent head injury to pupil testing predicted latency of constriction onset for each eye in those reporting head injury (right eye: adjusted R2 = 0.23, P = 0.02; left eye: adjusted R2 = 0.26, P = 0.01).

Conclusions: Dynamic pupil parameters elicited with a bright white stimulus were not predicted by history of mTBI. Time from most recent mTBI to date of pupil testing may partially predict latency of pupil constriction, and longer times from most recent mTBI to date of pupil testing may be associated with slower redilation velocities. However, the influence of age on the association between time from most recent mTBI and velocity of redilation in this study sample is unknown.

Keywords: mild traumatic brain injury, pupil dynamics, pupillography

Introduction

Quantification of pupil dynamics in routine practice is possible with currently marketed FDA-approved clinical instruments. Using various technologies, global dynamic pupil parameters and objective pupil perimetry have been incorporated in studies of glaucoma,[1-5] multiple sclerosis,[6-8] age-related macular degeneration,[9] head injuries,[10] and other disorders.[11-16] Furthermore, researchers and clinicians in areas outside of vision/eye care are using pupil dynamics for diagnosis and management of neurologic and systemic dysfunction.[17-19] Assessment of dynamic pupil responses in both vision and systemic health care is likely to gain popularity due to the objective nature of the data collection. Clinicians would benefit from knowing whether a mild traumatic brain injury (mTBI) is likely to have

long-term effects on dynamic pupil responses that could make interpreting pupil data for the purpose of diagnosis/management of other disorders, such as glaucoma, difficult.

A recent study on pupil dynamics supports Hilz's hypothesis that central autonomic dysfunction lingers in mTBI.[20] Thiagarajan et al. reported slowed pupil dilation dynamics and reduced maximum pupil diameters, peak velocities, and amplitudes in subjects with a history of non-blast-related mTBI compared to a control population.[10] The results from the Thiagarajan and Hilz studies suggest not only that abnormalities in pupil response dynamics can persist long after the traumatic event, potentially confounding interpretation of the data for diagnosis and management of non-traumatic disorders, but also that evaluation of pupil dynamics may serve to identify post-mTBI patients with prolonged autonomic dysfunction, thereby reducing mortality rates with appropriate referral for diagnosis and treatment.

To study the long-term effects of mTBI, study samples typically exclude subjects with other neurological disorders, those who are on medications that could affect the responses being measured, and those who are in the sub-acute period after the injury (15-45 days), thereby avoiding the potential for the natural healing process, which can take 6-9 months, from confounding the results.[10] For example, the mTBI subjects in the study by Thiagarajan et al.[10] were at least one year post-concussion, had no other neurologic diagnoses, and were not taking medications that could affect pupil responses. However, no information was reported on mean time from concussive event to date of data collection; therefore, estimation of duration of abnormal pupil responses in mTBI cannot be made from their data. Danna-Dos-Santos et al.,[20] in their study of post-concussion indices of oculomotor performance, reported a mean time from last injury to data collection of 43.11 months (SD = 52.45 months). Their results showed that mTBI subjects displayed abnormal saccades during smooth pursuit, diminished accuracy of saccades, and slower reaction to visual stimuli compared to their normal subjects. Other studies of the long-term effects of mTBI also have shown oculomotor dysfunction in mTBI patients that lingered for eight months or more post-injury.[21,22] Thus, the evidence suggests that some patients with mTBI may have detectable impairment of oculomotor function for several years after the most recent injury; whether abnormalities in dynamic pupil responses can be detected for several years post-mTBI is unknown.

The objectives of this study were 1) to characterize pupil dynamics in a sample of subjects not derived from a clinic population, 2) to determine whether differences in dynamic pupil responses were evident between those who had and those who had not experienced mTBI, and 3) to explore the effects of age, gender, history of mTBI, number of mTBIs, and time from most recent mTBI on dynamic pupil parameters.

Methods

Subjects

The research protocol conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Southern College of Optometry. Informed consent was obtained from all subjects prior to participation. No protected health information is included in this manuscript. Data collection took place during the annual meeting of the American Academy of Optometry in 2016, over a 2-day period in the exhibit hall research booth in conjunction with the Fellows Doing Research Special Interest Group. From the initial 287 participants volunteering, pupil data from 137 subjects (80 female, 56 male, 1 not reporting gender) were eligible and available for analysis.

Instrumentation

Binocular dynamic pupillary responses were collected with high-definition pupillography, using the RAPDx (Konan Medical, Inc.). Three instruments were used to expedite data collection during the 2-day collection window, all of which were calibrated prior to use. The stimulus selected for this study was a white light of approximately 330 candelas/square meter, 28 degrees in size, and 100 milliseconds in duration. The white light stimulus alternated between the eyes, with an interstimulus interval of 200 milliseconds. Pupil testing session duration ranged from 34 to 120 seconds in order to capture good responses to eight pairs of stimuli. Pupil images were captured with infrared light at a rate of 60 Hertz. Averaged data across the eight responses were used for the statistical analysis.

Testing Procedure

After completing demographics, health history, and vision symptom surveys, subjects were seated comfortably in front of the RAPDx and asked to look into the instrument, which was not illuminated except during presentation of the test stimulus.

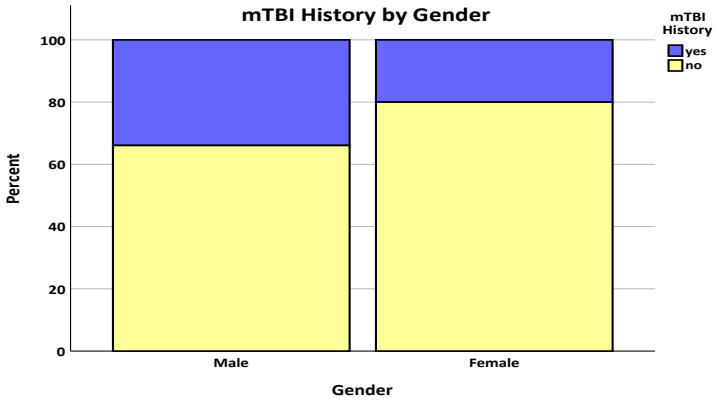

Figure 1. *Comparison of proportions of mTBI history across gender.*

No period for dark adaptation was given prior to pupil testing (similar to the set-up for clinical gross observation of pupil responses with a hand-held light source). Once the technician initiated testing, the stimulus was presented to each eye sequentially until the requisite eight pairs of good responses needed for analysis were obtained. The following pupil parameters were recorded for each eye: pre-stimulus maximum pupil diameter, latency to constriction onset, latency to maximum constriction, maximum constriction velocity, mean amplitude of constriction, and maximum redilation velocity. Additionally, the proportion of constriction relative to the pre-stimulus maximum pupil diameter, the interocular difference in constriction amplitude, and the interocular difference in latency to constriction onset were calculated for each subject.

Data Analysis

Subjects who reported the following conditions were excluded from data analysis: a history of systemic or ocular disease that could affect vision, pupil responses, or the autonomic nervous system (e.g., diabetes mellitus, Horner's syndrome, glaucoma, Parkinson's disease); known history of stroke, brain tumor, or brain surgery; and current medications that could affect vision, pupils, accommodation, or the autonomic nervous system (e.g., amphetamines, muscle relaxants, autonomic stimulators/relaxers). All subjects whose pupil data were collected on one of the instruments were excluded from analysis because an error in instrument set-up prohibited retrieval of their data. A few subjects were excluded due to errors of data input. Thus, of 287 subjects presenting for participation, the data for 137 subjects was available and eligible for analysis. Multiple linear regression analysis was applied using SPSS V 21.0 (IBM). Non-parametric statistics were used when assumptions for parametric statistics were not met. All reported P values are two-tailed.

Results

Of the 137 subjects included in the analysis, 35 reported a history of mTBI. The mean age of the subjects with a history of mTBI was 36.4 ± 14.5 years (95% CI: 31.3 – 41.5 years), and the mean age of the subjects without a history of mTBI was 33.1 ± 11.3 years (95% CI: 30.9 – 35.3 years). Mann-Whitney U test showed that the distributions of ages in the two groups were not significantly different (Z = -0.66, P = .51). Fifteen subjects reported more than one head injury. Of those 15, 6 reported three head injuries; no subject reported more than three head injuries. Mann-Whitney U test showed that the distributions of ages for those who reported one mTBI and those who reported more than one mTBI were not significantly different (Z = -1.50, P = .14).

The median self-reported time interval between the most recent head injury to the date of pupil data collection for this study was 9.0 years, and the range was from 3 months to 66 years. The subject who reported that the most recent head injury had occurred 66 years before the time of data collection was identified as an outlier, since this data point is more than 3.29 standard deviations from the mean. With the outlier removed, the median time from most recent injury to date of pupil data collection was 8.5 years, and the range was 3 months to 28 years.

No significant difference in the proportion of males versus females reporting a positive history of mTBI was found (Z = -1.76, P = .08, Figure 1). Of the 35 subjects reporting a positive history of mTBI, 19 were male (54.3%). With respect to the number of mTBI, 15 subjects (5 male and 10 female) reported more than one mTBI. The binomial probability that 5 or fewer males would report more than one mTBI is not significantly different from 0.543 (P = 0.17), suggesting that no gender difference was found in the proportion of subjects reporting more than one mTBI.

Linear regression analysis of the dynamic pupil parameter data from all subjects showed that none of the individual pupil parameters assessed for either eye could be predicted based on a history of mTBI (Figure 2a-f and Table 1). The number of head injuries approached significance for predicting the latency of constriction onset for the right eye (P = 0.06), but not for the left eye (P = 0.15). Time interval from most recent head injury to time of pupil testing was significant for predicting only the latency of

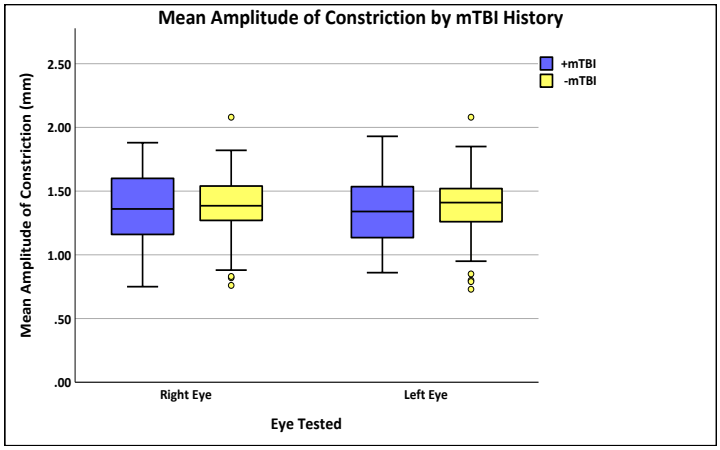

Figure 2a

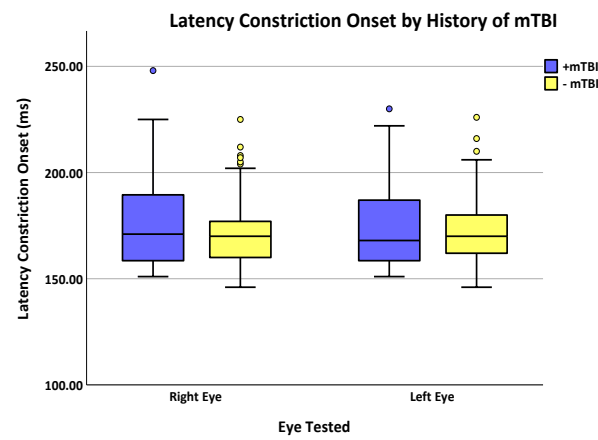

Figure 2b

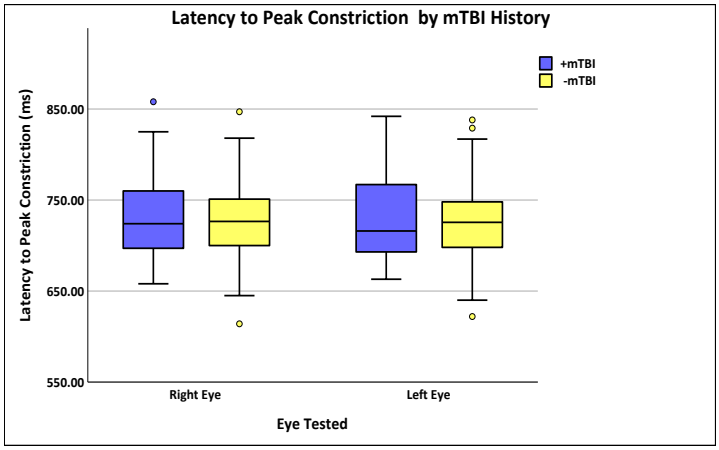

Figure 2c

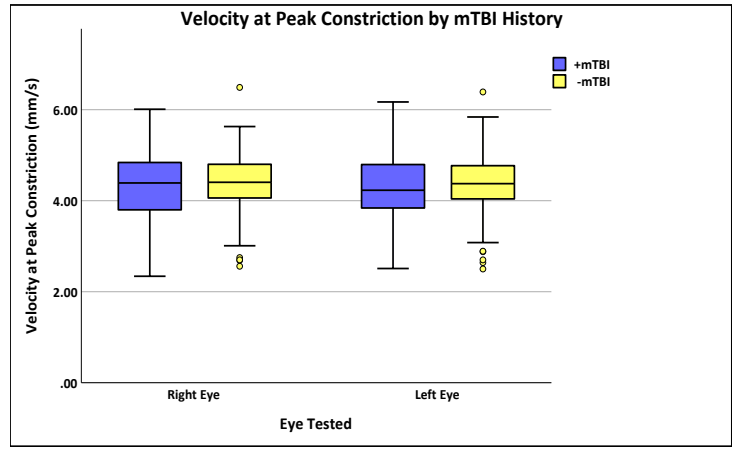

Figure 2d

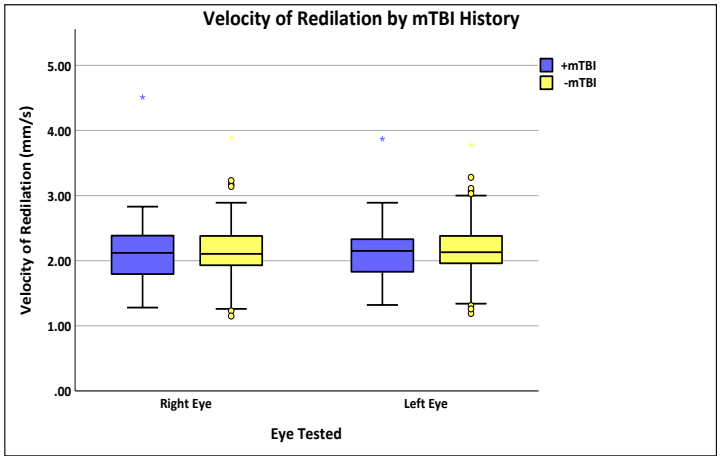

Figure 2e

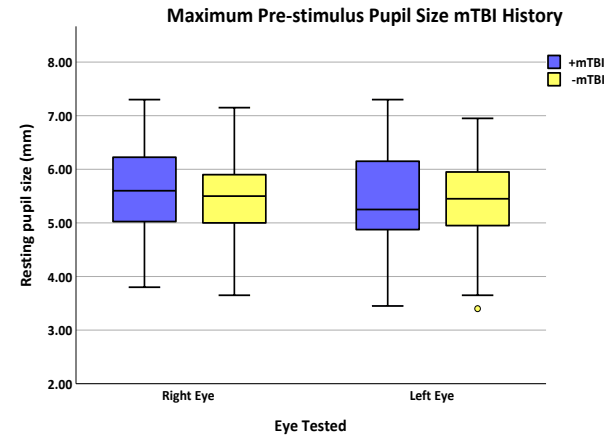

Figure 2f

Figure 2a-f. *Comparisons of dynamic pupil response parameters across mTBI history groups. (a) Amplitude of constriction; (b) Latency to constriction onset; (c) Latency to peak constriction; (d) Velocity at peak constriction; (e) Velocity of redilation; (f) Maximum pre-stimulus pupil diameter*

Table 1. Summary of Dynamic Pupil Responses

Pupil Parameter	Head Injury Group	Mean (SD)-right eye	95% CI for mean, right eye	Mean (SD)-left eye	95% CI for mean, left eye	P value, right eye	P value, left eye
Amplitude of constriction (mm)	-mTBI	1.38(0.23)	1.35-1.41	1.38 (0.23)	1.33-1.43	0.51	0.42
	+mTBI	1.35(0.27)	1.28-1.41	1.34 (0.26)	1.25-1.43		
Latency, constriction onset (ms)	-mTBI	172(15)	169 - 175	173 (16)	169 - 176	0.15	0.32
	+mTBI	172(22)	169 - 184	176 (21)	169 - 183		
Latency, peak constriction (ms)	-mTBI	729(44)	720 - 737	728 (44)	719 - 737	0.52	0.78
	+mTBI	734(49)	717 - 751	730 (48)	714 - 747		
Velocity, peak constriction (mm/s)	-mTBI	4.26(0.69)	4.23 – 4.50	4.37 (0.68)	4.23 – 4.50	0.65	0.50
	+mTBI	4.30(0.83)	4.01 – 4.58	4.27 (0.80)	4.00 – 4.55		
Velocity of redilation (mm/s)	-mTBI	2.16(0.43)	2.07 – 2.24	2.16 (0.43)	2.08 – 2.25	0.95	0.82
	+mTBI	2.16(0.58)	1.96 – 2.36	2.15 (0.49)	1.98 – 2.31		
Pre-stimulus maximum pupil diameter (mm)	-mTBI	5.45(0.69)	5.31 – 5.58	5.41 (0.70)	5.27 – 5.55	0.4	0.77
	+mTBI	5.55(0.94)	5.23 – 5.88	5.45 (0.94)	5.13 – 5.78		

-mTBI: No history of mild traumatic brain injury, +mTBI: Yes history of mild traumatic brain injury, SD: standard deviation, CI: confidence interval, mm: millimeter, mm/sec: millimeters per second, ms: milliseconds,

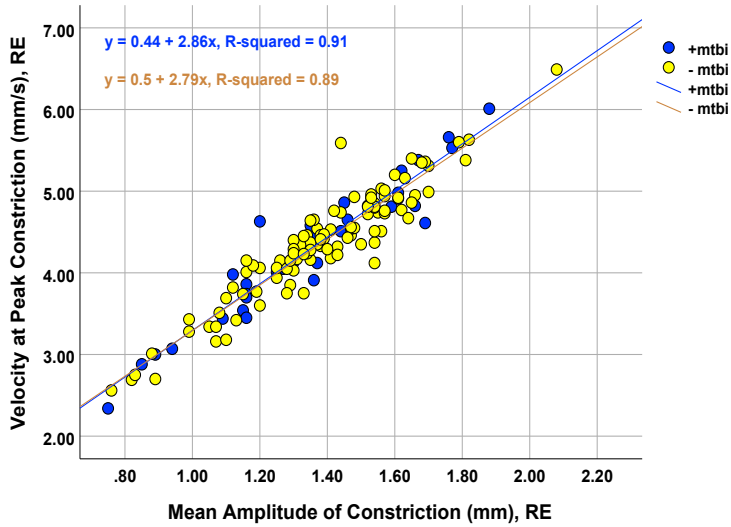

Figure 3a

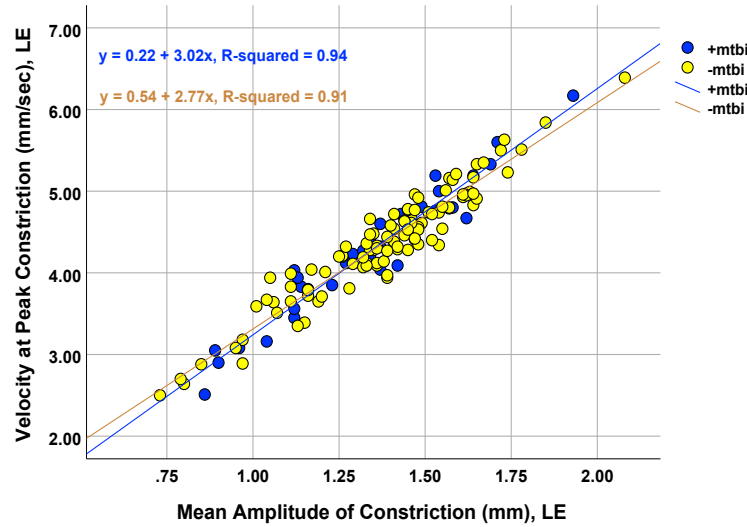

Figure 3b

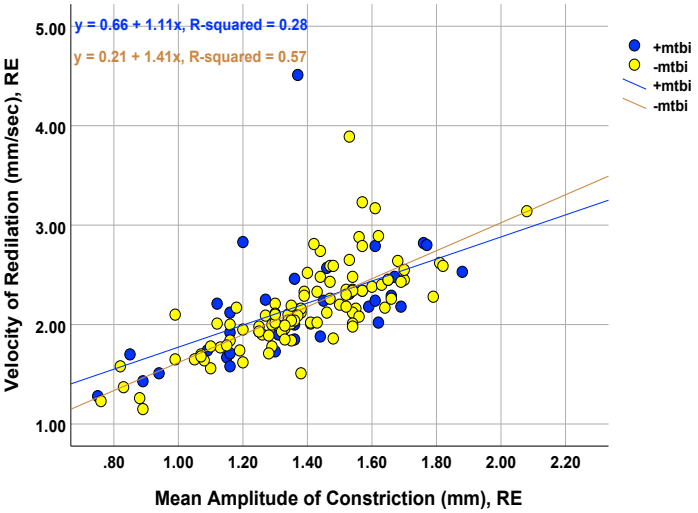

Figure 3c

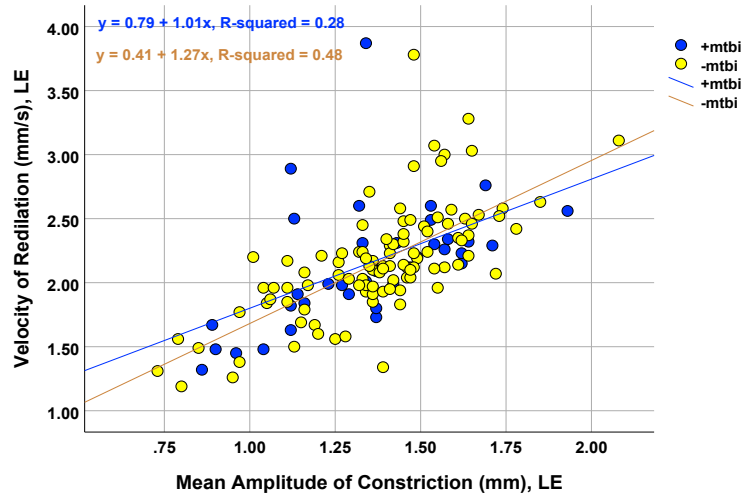

Figure 3d

Figure 3a-d. *The main sequences for peak velocity of pupil constriction (a-b) and velocity of pupil redilation (c-d) plotted against mean amplitude of constriction are shown for the right and left eyes, separately determined for those with (blue) and without (brown) a history of mTBI*

Table 2.Coefficients of Main Sequence Regression Lines: Summary of Statistics

Main Sequence	Coefficient, +mTBI	Coefficient, -mTBI	T (mTBI Hx * amplitude of constriction)	Significance (2-tailed P)	95% CI (mTBI Hx * amplitude of constriction)
Velocity at Peak Constriction vs Amplitude of Constriction, RE	2.86	2.73	-0.35	.73	0.42 – 0.29
Velocity at Peak Constriction vs Amplitude of Constriction, LE	3.02	2.77	-1.53	.12	-0.56 – 0.07
Velocity of Redilation vs Amplitude of Constriction, RE	1.11	1.41	1.13	.26	-0.22 – 0.82
Velocity of Redilation vs Amplitude of Constriction, LE	1.01	1.27	.98	.33	-0.27 – 0.88

+mTBI: yes history of mild traumatic brain injury, -mTBI: no history of mild traumatic brain injury, T: t-test statistic, CI: confidence interval, RE: right eye, LE: left eye,

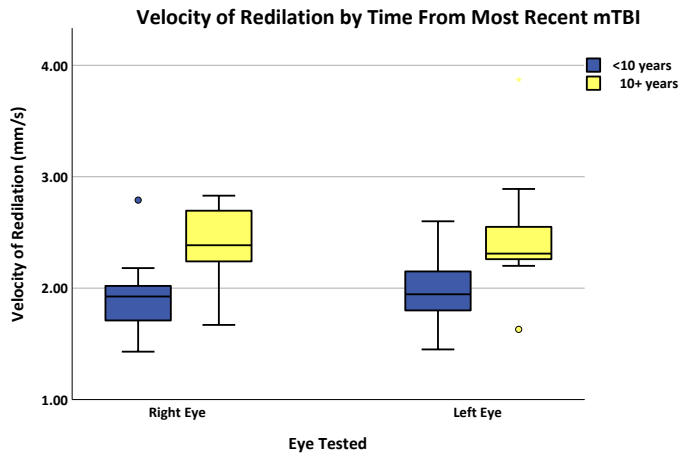

Figure 4. *The mean velocities of pupil redilation for right eye (RE) and left eye (LE) are plotted for two groups defined by time from most recent mTBI: less than 10 years (blue) and 10 or more years (yellow).*

constriction onset of each eye (right eye: P = 0.02, R2 = 0.214; left eye: P = 0.02, R2 = 0.187). Gender was not a predictor for any of the pupil parameters; however, age was a strong predictor of several pupil parameters (mean amplitude of constriction, right eye and left eye; latency of constriction onset, right eye and left eye; velocity at peak constriction, right eye and left eye; velocity of redilation, right eye and left eye; pre-stimulus maximum pupil diameter, right eye and left eye; all P values <0.01). Multiple linear regression showed that age and time from most recent head injury to pupil assessment were significant predictors of the latency of constriction onset for each eye in those reporting head injury (right eye: adjusted R2 = 0.23, P = 0.02; left eye: adjusted R2 = 0.26, P = 0.01).

Figure 3 shows the comparison of the "main sequence" for peak velocity of pupil constriction (a-b) and for velocity of redilation (c-d) between subjects without and with a history of mTBI. No significant difference was found in the coefficients of the regression lines between those with a negative vs. a positive history of mTBI for all conditions tested (Table 2). The correlation coefficients for the main sequences were higher for peak velocity of constriction data than for velocity of redilation data for both (+)mTBI and (–)mTBI groups.

Plots of individual pupil parameters against time from most recent mTBI did not reveal any linear relationships except for latency of constriction onset for each eye, as noted above. To assess for an association between time from most recent mTBI to pupil assessment and the dynamic pupil parameters, Spearman's rank-order correlations were performed. The following correlations with time from most recent mTBI to date of pupil assessment were significant: 1) velocity of redilation, right eye (rs = .55, P = .003) and 2) velocity of redilation, left eye (rs = .50, P = .008); see Figure 4. The Spearman's rank-order correlation between time from last mTBI to date of pupil assessment and age was not significant (rs = .30, P = .14).

Discussion

This study found that none of the dynamic pupil parameters for either eye as assessed with a bright white stimulus (as measured by the RAPDx) could be predicted by a past history of mTBI. Additionally, the time interval from the most recent mTBI to the date of pupil testing may partially predict the latency of pupil constriction, and longer times from most recent mTBI to date of pupil testing may be associated with slower pupil redilation velocities. However, the influence of subject age on the association between

time from most recent mTBI and velocity of pupil redilation in this study sample is unknown.

In their 2017 review, Ciuffreda et al. outlined the normal static and dynamic pupillary light responses and reported on studies evaluating changes from normal in those who have experienced mTBI.[23] From their literature review and their own work, they concluded that most mTBI patients demonstrate negligible static or dynamic pupil asymmetry. With respect to parameters of an individual pupil's response, however, several differences from normal[24] have been found in mTBI patients, including: average constriction velocity (slower), average dilation velocity (slower), constriction latency (delayed), average constriction amplitude (smaller), and maximum pupil diameter (smaller).[10,23] They also noted that differences in pupil parameters in head injury patients across studies may be attributed to different stages after injury in which the pupils are tested (i.e., acute, sub-acute, or chronic). In a study with a larger number of subjects and more varied stimulus parameters (e.g., luminance and chromatic differences), four pupil parameters discriminated between mTBI and non-mTBI subjects for all tested conditions: maximum pupil diameter, minimum pupil diameter, average constriction velocity, and pupil dilation velocity.[25] The present study did not find significant differences in any of the pupil parameters measured between mTBI and non-mTBI subjects with a high-intensity, white-light stimulus. Whether the ability to adjust the stimulus parameters to tease out more subtle changes in pupil parameters would have changed our results is unknown.

The differences found between this study and previous studies may be due in part to differences in the subject pools used. In the 2015 Thiagarajan study, the subjects were recruited from a vision rehabilitation center, suggesting that they had been diagnosed with and possibly treated for ocular/visual symptoms associated with the mTBI. The present study used self-reporting for the mTBI diagnosis and did not collect information about whether the subject had received any type of vision or other therapy after the mTBI. Thus, the Thiagarajan study sample may have been more symptomatic than our study sample. Additionally, although their subjects were at least one year post-mTBI, the authors did not give a median or range of time between injury and time of data collection. Since our median time of 8.5 years may have been larger than their median time post-mTBI, the difference in time from last injury may also have contributed to the different results found between the studies.

Another difference between this study and previous work is the mean number of head injuries in the mTBI subjects. The mean number of head injuries in the present study was 1.6; the mean number of head injuries in the Danna-Dos-Santos et al. study was 2.5.[20] Thiagarajan et al. did not report the number of head injuries,[10] whereas Truong et al. reported two or more head injuries in more than half of their subjects.[25] Tyler et al. used subjects reporting only one past mTBI, but time from injury to oculomotor testing varied from subacute to chronic intervals.[26] Additionally, no information was collected about the amount of time between head injuries when multiple events were reported for the present study or the studies referenced above. Thus, whether second-injury syndrome[27] or repetitive head injury[28] influenced the pupil parameters in the present and other studies is unclear. The variation in reporting of the number of head injuries, the time interval between head injuries (when relevant), and the time from the most recent event to the time of testing contribute to the difficulty of between-study comparisons. Longitudinal studies, using subjects who have experienced similar types and degrees of injury, are needed to clarify the effects of mTBI on dynamic pupil and oculomotor parameters.

Differences between this study and previous work may be partly due to differences in the environments in which the data were collected. The referenced studies typically collected pupil responses in well-controlled laboratory settings, whereas our data were collected in a noisy public space from mid-morning to early evening. Additionally, we did not control for fatigue or for alcohol and/or caffeine ingestion prior to data collection. Since alcohol, caffeine, fatigue, and stress can influence the pupil responses via autonomic system stimulation,[14,29-31] not controlling for them may partially explain our failure to find differences in pupil parameters between those with versus without a history of mTBI.

Also potentially contributing to differences in results found between this and other studies is the number of technicians employed for data collection. Although the present study used a standard clinical protocol, more than 20 individuals were involved in data collection, most of whom were trained on instrument use just before their data collection session. Although technicians were informed how to instruct the subjects for the test prior to data

collection, the use of multiple, novice technicians could inadvertently have led to increased subject anxiety during testing if the technicians appeared uncertain or were unable to answer subjects' questions about how the instrument worked. Increased anxiety has been shown to affect pupil responses.[32] Moreover, 11 subjects were lost due to errors of data input, and all of the data from one of the instruments were lost due to incorrect initial set-up that prohibited retrieval of interpretable data. In spite of the data loss, the 137 subjects with complete data were sufficient for statistical analysis.

In our group of 35 subjects reporting a positive history of mTBI, the proportions of males and females were similar. Research on gender differences in concussion rates has produced conflicting results, with the differences appearing to be at least partially related to differences in the study samples. A literature review specifically of sports-related concussion and gender revealed several studies reporting higher injury rates for females than for males.[33] The higher rates for mTBI in female athletes have been attributed to differences in female head and neck anatomy that make females more vulnerable to injury,[34] as well as to psycho-social factors that lead to greater reporting of injuries and symptoms by females.[35,36] Being denied the ability to "return to play" has been identified as a factor that lowers mTBI rates for males because of their failure to report symptoms.[38] Since this factor was absent in our study sample, a higher proportion of males may have reported mTBI in this study compared to the sports concussion studies. In contrast to the sports-related concussion reports, a meta-analysis of TBI in the general adult population of developed countries that included all causes of TBI concluded that males had more than twice the odds of having had TBI than females.[37] Since the present study did not specifically inquire about the cause of the reported mTBI, a mixture of reporting sports-related (with greater female/male ratio) and non-sports related (with greater male/female ratio) mTBI in the study sample, which likely occurred, would explain a failure to find a gender difference in mTBI reporting in this study.

The present study also did not find a gender difference in the proportion of mTBI subjects reporting more than one mTBI. Although several studies report that having experienced a recent mTBI is a risk factor for a repeat event,[39-42] gender differences in this risk factor have not been explored. A review of the literature produced only one study that reported gender differences in repetitive TBI. In 2016, Fakharian et al. reported on 41 cases of repetitive TBI, which comprised 2.5% of all TBI cases presenting to an emergency department of a hospital in Iran over a one-year period.[43] Of the 41 cases, 3 (7.3%) were female. The proportion of females experiencing repeat TBI may have been small due to the main cause of the repeat TBI in their subjects – road traffic accident involving a motorcycle. (The law in Iran presently does not permit women to drive a motorcycle.[44])

No gender differences in any of the dynamic pupil parameters were found in the present study, for either the mTBI or non-mTBI subjects. With respect to other studies of oculomotor and/or pupil function in mTBI subjects, neither Danna-Dos-Santos nor Truong et al. reported the gender of their subjects.[20,25] Thiagarajan et al. reported the gender of their subjects but did not statistically analyze pupil responses across gender.[10] Capo-Aponté et al. also did not report the gender in their study of pupil dynamics in blast-related mTBI.[45] Failure of the present study to find a gender difference in pupil function is consistent with the failure to find a gender difference in photosensitivity in mTBI subjects.[46] However, gender differences have been found in some post-mTBI measures of the brain, such as cortical thickness,[47] functional connectivity between the left orbitofrontal cortex and the right midfrontal cortex (fMRI),[48] and fractional anisotropy in the uncinate fasciculus (diffusion tensor imaging).[49] A longitudinal study of pupil dynamics in a larger sample of mTBI subjects, using stimuli of different wavelengths and intensities, would help clarify whether gender differences exist in recovery of pupil responses over time.

Analysis of individual pupil parameters against time from most recent mTBI in the present study did not reveal any linear relationships when controlling for age, except for latency of pupil constriction, right eye and left eye. Given that 1) no information about severity of head injury or duration of symptoms from the subjects was obtained, 2) the length of time from most recent mTBI to pupil testing for most subjects was one year or longer, and 3) the pupil size influences the dynamic pupil parameters, the failure to find a linear predictive relationship for most of the dynamic pupil parameters in our mTBI subjects is not surprising. Since the variability in the latency of pupil constriction data in the present study is partly explained by the time from most recent mTBI, this dynamic pupil response parameter may be the last one to recover in mTBI. We did find an association between redilation velocity and time from most

recent mTBI, as shown in Figure 4. However, the lack of sufficient subject numbers in multiple age groups prohibited the ability to control for the effects of age on redilation velocity.

The possibility that pupil dynamics may be altered long after the date of a head injury is suggested by studies that have shown that other types of abnormal responses may linger in head injury. Patients who have sustained a head injury have increased long-term mortality rates, the etiology of which is unknown.[50] Hilz et al. hypothesized that "central autonomic network dysfunction may contribute to cardiovascular dysregulation and increased mortality."[20] To test whether a subtle autonomic dysfunction is present in post-mTBI patients, Hilz et al. used eyeball pressure stimulation to impose a purely parasympathetic cardiovascular challenge while monitoring respiration, electrocardiographic parameters, and blood pressure (indicators of autonomic function). Although normal controls showed the appropriate shift in autonomic function towards parasympathetic predominance in response to the challenge, post-mTBI patients demonstrated increased blood pressure but could not increase parasympathetic heart rate modulation, suggesting that they were experiencing a paradoxical sympathetic reaction. They concluded that these findings "support the hypothesis that central autonomic dysfunction might contribute to an increased cardiovascular risk, even years after mTBI."[20] Whether pupil responses were different or were affected differently by the eye pressure stimulation in the post-mTBI subjects compared to the controls in the Hilz et al. study is unknown. Given that pupil responses are controlled by the autonomic nervous system, abnormal response dynamics may reflect an autonomic imbalance that, if chronic, could precipitate adverse cardiovascular events.[51]

Conclusion

Dynamic pupil responses in long-time post-mTBI subjects, measured with a bright white stimulus, appear to be similar to those of non-mTBI subjects when controlled for age. However, since latency of pupil constriction appears to be correlated with time from most recent mTBI, a cautious approach is recommended when using latency of pupil constriction for diagnosis and management of non-mTBI disorders in patients with a history of mTBI. Longitudinal studies to explore the time course for recovery of dynamic pupil response parameters are needed. Understanding the long-term effects of mTBI on dynamic pupil responses may prove useful in the identification of patients with chronic autonomic imbalance.

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