Evaluation of Reflex and its Applications in Medicine

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Abstract

The pupillary light reflex (PLR) is an important indicator of cognitive capability that is widely utilized in medicine today. Reflex is a mobile solution to assess PLR by only utilizing the camera and flash present in an iOS device. The present disclosure encompasses a full analytical analysis regarding the operability of Reflex and how it can be utilized to assist in the management of neurological disturbances, injury or indicators.

1. Introduction

Historically, the pupillary light reflex (PLR) has been an important subjective analysis technique for medical personnel for over a century [1]. Pop culture references to PLR testing have placed it front and center into the attention of the public making it a noticeable test both in practice and experimentation. The last three decades have heightened exposure of a technique described as quantitative pupillometry or quantitative analysis of the pupillary light reflex (qPLR). Efforts to characterize PLR has led to the development of standalone technology that can use high-definition infrared cameras to reliably monitor PLR [2]. qPLR is a difficult task in ambient lighting conditions so the use of infrared spectrum light (700 to 1000 nm) to adequately distinguish the characteristics between the pupil and iris is important for today's thresholding methodologies.

As an example Figure 1 shows images contain-

ing iris taken in visible and near infrared light spectrum. The first row of both parts (a and b) of Figure 1 show irides taken in visible light and second row show iris captured in near infrared light using the Iritech IriShield USB sensor. It is easy to observe from Figure 1 that inner boundary of iris which outlines the pupil in RGB color space taken in visible light on individuals with dark iris is objectively harder. Given that dark brown is the dominant color in human species in many parts of the world according to [3], measuring PLR in visible light is a challenge that Reflex surmounts to provide reliable, repeatable results in ubiquitous smart phones which is a cost-effective solution.

Infrared camera systems provide clear and highresolution information for analysis but lose meta information relating to colorimetric data present in the subject's iridial region. This grey-scale union averages what was once relevant information [5]. qPLR analysis systems that operate utilizing standard complementary metaloxidesemiconductor (CMOS) sensing matrices typically struggle with accuracy due to their inability to distinguish between dark colors and the black region of the iris. Examples using high-definition CMOS cameras, web cameras, and integrated device cameras have all been attempted but most usually fail in low contrast image sets [6]. Nonetheless these techniques are still being evaluated for practical deployment without proper characterization of their limitations.

Reflex is the world's first fully functional mobile pupillometer that requires no additional hardware. The distinguishing aspect between Reflex



(b) Dark color irides

Figure 1. Comparison of RGB iris images and near infrared images [4]

and other attempts of mobile systems is Reflex's ability to operate with a low error rate in ambient, visual spectrum, conditions. Management of qPLR testing is typically long and inconvenient due to device size or unreliability. An accurate mobile system overcomes these challenges by democratizing qPLR software across previously established devices and integrating frontier computer vision systems.

2. qPLR Current Methods

Current qPLR methods are the product of a need for clinical pupillometric analysis to advance both research and diagnostic methods. Typically, qPLR systems are produced in a goggle or hand-held form factor with others representing tabletop systems. The most widely recognized unit in qPLR is Neuroptic's NPi-200 system, as pictured in Figure 2 (left), that is a hand-held unit with interconnectivity to electronic medical record (EMR) systems. Base quotation of this unit is between 4,500 and 9,000 USD [7] with additional features available for purchase. Neuroptic's NPi-200 system is a Class I medical device as listed under 21

CFR 886.1700 [8].

The NPi-200 utilizes an infrared camera sensing matrix for image acquisition that is processed as a linear time-series for further parameterization. A defining characteristic of the system is it's ability to report a a calculated metric identified as the Neurological Pupil index (NPi) Pupil Reactivity Assessment Scale. The algorithm for calculating NPi is not publicly available and Neuroptics does not offer transparency in its correlative scale or its clinical significance. Clinical consensus is to utilize only the one-to-one characterized parameters that are associated with ground-truth responses to prevent information mischaracterization in a consolidated score. Reported accuracy of the NPi-200 is +/- 0.03 mm but further data characterization against ground-truth examples are not reported or identified [8].

Another recent qPLR system has been produced by clinical researchers at the University of Washington targeted for the evaluation of individuals with suspected head injury or mild traumatic brain injury (mTBI), otherwise known as concussion. This qPLR mobile App, PupilScreen as pictured in Figure 2 (right), uses a shield encompassing an iOS device that is held horizontally. It then utilizes the flash and integrated CMOS camera to capture PLR information. PupilScreen uses a preestablished trained convolutional neural network to evaluate PLR. Machine learning is used to segment the pupil area from the iris and it then measures the diameter of the segmented area via a fitting algorithm. There are no reported accuracy values for the PupilScreen, software but a publication conclusively determines average difference for pupil center and pupil diameter as 3.46 px and 2.00 px, respectively [7]. PupilScreen is currently not for sale and is only a research tool due to freedom to operate limitations with the United States Patent and Trademark Office (USPTO). Many other systems exist outside of these two notable units but typically do not have large market share or reliable performance metrics.



Figure 2. Left: NPi-200; Right: PupilScreen

3. qPLR with Reflex

Reflex is a qPLR innovative software tool for iOS devices produced by brightlamp Inc. that requires no additional hardware. Its main function is to acquire a series of images from the internal CMOS camera found in iOS devices that have a PLR response available for measurement. This PLR response is initiated by the light emitting diode (LED) found on the back of the device in close proximity to the camera. Reflex has a simple UI shown in Figure 3 that is unlike traditional qPLR tools that have custom interfaces that must work appropriately with the given form factor. This clean UI allows for intuitive control of the unit as well as simplified data management.

Various test alterations can be done with Reflex including adjustment of recording time, flash time, and brightness. Versatility is a key aspect of Reflex as it is a mobile solution that is both convenient and powerful. Test acquisition times are between 1 and 5 seconds as adjusted within the tool. Processing times are approximately 1 second for the maximum recording durations (5 seconds). Once the video has been delivered to a secure server a sequence of processing steps occurs to extract the relevant PLR information.

4. Reflex Pipeline

Figure 4 outlines the technical pipeline of Reflex for video analysis and qPLR extraction. Reflex records a video of a subject's eye at 30 Hz which is parsed into images and is passed into a trained object detector. Reflex has a custom detection architecture to allow for rapid identification of an iris



Figure 3. Reflex main test screen and results UI



Figure 4. Reflex pipeline

while also detecting partial irises as a result of eyelid occlusion. The detector classifies images based on two outcomes; has an iris or doesn't have an iris. While binary, the detector has the ability to classify occlusion due to inter-series fallout of iris detection. Provided there is an iris in the image, the detector is responsible to locate the iris and supply rectangular co-ordinates of the object of interest in the image. The detector and classifier were trained with 5000 positive images containing an iris and 500 negative images without an iris.

Comparing number of frames in the video which encompassed an iris to a predetermined threshold, Reflex decides whether a video is capable of pro-

Table 1. Haar Detector vs. Custom Iris Detector

Туре	Accuracy	Error rate	mean IoU
Custom Det.	96.9%	3.1%	0.814
Haar Det.	89.2%	10.8%	0.790

ducing sufficient data to produce a qPLR result. Subsequently, the predictions of iris location on videos which passed the threshold test are then cleaned using first and second order statistics in an outlier detection phase. The registration phase stabilizes the frames in the video to arrive at a single reference axis for the entire video. Post this, our proprietary algorithm determines the pupil diameter for each frame.

5. Reflex Results

Two different types of detectors were trained that include a Haar detector and brightlamp's custom detector. Test accuracy, error rate, and mean intersection over union (IoU) values are provided in Table 1 below. The test set consisted of 1400 positive images with an iris and 700 negative images without an iris.

Manual annotations were conducted for 600 images by a computer vision professional to provide ground-truth pupil diameter values. Ground truth values were measured using a commercial annotation tool and taken for both pupil and iris dimensions. Annotations give rectangular coordinates that bound the two objects and its dimensions are utilized in characterization of the accuracy of Reflex. Reflex's scaled values are compared to ground-truth scaled values to determine accuracy outside of detector bias. This comparison is shown for selected videos in Figure 5 across the image time series (seconds) post outlier detection. Predicted values from Reflex trend closely with ground-truth values and have a mean average error (MAE) of 2.9%.

Referential spatial locking is conducted using the custom detector to convert dimensionless values to the standard pupillometer measurement, millimeters. The detector has a bias equal to 2x its win-



Figure 5. Ground-truth (GT) vs. Reflex results (Pred)

dow value which is translated into the qPLR timeseries values. This bias slightly increases the MAE of the time series fit but not to a substantial degree. Reflex's millimeter time series plots have a MAE value of 0.75 mm as compared to ground-truth values. Typically, the detector has a positive (+) bias to the analysis and future correction methods can be deployed to minimize the gap even more.

A parametric analysis of Reflex's output was conducted and compared to ground-truth values. These parameters include: Latency, Maximum Constriction Velocity (MCV), Average Constriction Velocity (ACV), and Time to Constriction (TC) with their values shown in Table 2. Additionally, an error analysis was conducted for the parameters as compared to calculated ground-truth values with the concluded MAE values in Table 3.

Further statistical evaluation of Reflex's output shows that it has a variance of 0.08 mm^2 from ground-truth values and a standard deviation of 0.26 mm.

6. Neural Pathway of PLR

The neural pathway of the pupillary light reflex has a complicated I/O structure that contains both afferent and efferent limbs. Sensory input follows the afferent limb where the optic nerve and retina are contained and connect to the pretectal nuclei located in the midbrain. The pretectal nuclei project to the Edinger-Westphal nuclei (EWN) where each pretectal nucleus has dual input to each EWN [9]. This interconnectivity both ipsilaterally and contralaterally allow for both pupils to react

	1	2	3	4
Latency (sec)				
GT	0.133	0.133	0.200	0.133
Pred	0.133	0.200	0.133	0.133
MCV (mm/sec)				
GT	2.574	5.383	3.391	5.471
Pred	2.918	4.821	4.423	3.237
ACV (mm/sec)				
GT	0.948	1.595	1.524	1.264
Pred	0.882	1.428	1.385	0.955
TC (sec)				
GT	1.033	1.996	0.833	1.900
Pred	1.200	1.966	1.267	1.900

Table 2. Calculated Parameters for Ground-Truth & Reflex Results

Table 3. Mean Avg. Error of Reflex Parameters from Ground-Truth

Parameter	MAE		
Latency	0.034 sec		
MCV	1.111 mm/sec		
ACV	0.170 mm/sec		
TC	0.150 sec		

even if only one is stimulated. Consensual response is what is described as the contralateral iris constricting from light stimulus [10]. There are two efferent limbs that support output to the eye and are in parallel to the oculomotor nerve. The two efferent limbs are categorized under the sympathetic and parasympathetic pathways for signal output. The parasympathetic pathway constricts the iris while the sympathetic pathway dilates. Bright stimulus follows to the ciliary ganglion where it moves to the parasympathetic postsynaptic neuron to release norepinephrine to relax the iridial sphincter. Dim stimulus follows the cervical ganglion where it moves to the sympathetic postsynaptic neuron to release norepinephrine to constrict the iridial sphincter [11].

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7. qPLR Clinical Significance

Clinical use of the pupillary light reflex is valuable due to complex interconnectivity of the PLR pathway. It is a useful diagnostic tool in evaluating both sensory and motor functionality. Absence of a PLR response can indicate sensory damage that is not allowing proper input to reach the pretectal nuclei so constriction can ensue. Additionally, monitoring of the consensual response of the contralateral iris from stimulus can give insight into oculomotor output and potential nerve damage in the parasympathetic pathway [10]. Abnormal pupillary light reflex can also be a direct indicator of potential brain stem injury, drug usage, mild traumatic brain injury, neurodegeneration and many other neurological dysfunctions.

Quantitative analysis of the pupillary light reflex can lend itself to characterizing non-binary disturbances that portray themselves via PLR. Many clinical uses of PLR are subjective and lack the granular monitoring to track progression, degree of injury, or neurological fluctuations. qPLR is a reliable way to track on a more quantifiable level the changes relating to PLR response. Proper quantization can even lend itself to stroke and legion triangulation in the brain. Mapping responses based of which neurological pathway is responding abnormally can locate, with high precision, any mass before medical imaging [12].

8. qPLR Clinical Applications

Quantitative pupillometry has been a primary focus of research for the past three decades. Many recent findings have led to breakthrough utilizations of qPLR that have led to increase patient outcomes and detection rates of neurological disturbances.

8.1. TBI and Concussion

Almost 4 million sports-related traumatic brain injuries (TBIs) occur in the United States each year, with most being mild TBIs (mTBI), better known as concussions [13]. Acute mTBI symptoms make diagnosis easier. In many cases individuals present as asymptomatic, which can result in a missed di-

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agnosis. As a result, the actual number of annual sports-related mTBIs is underestimated [14]. An undetected mTBI is problematic because it increases the chances for added injuries, prevents individuals from taking the proper steps for recovery, and can lead to chronic symptoms going undiagnosed and/or untreated. Neurological and cognitive examinations, the current clinical standard for mTBI diagnosis, are subjective and often inaccurate. One method for objectively measuring cognitive changes after an mTBI is qPLR. Changes in pupil response have been correlated with brain stem and hypothalamus injuries [15], blast-induced mT-BIs [16], and non-blast induced mTBIs[17][18].

8.2. Fatigue

Subsets of the population are suffering from excessive fatigue due to improper sleep management, malnutrition, and over exertion. Fatigue can slow the synaptic response of the brain's parasympathetic pathway causing a noticeable change in the PLR of a subject. Excessive daytime sleepiness (EDS) in adults can be characterized by PLR latency and constriction velocity and closely compare to self-reported fatigue levels [19]. In many cases fatigue can impact emotional status which can lead to adverse reactions in times of significant stress. Sleep deprivation and its impact on pupillary activity has been correlated to increased reactions to negative imagery [20]. Even broader studies have shown a distinct relationship between time-of-day fatigue and pupillary response factors [21].

8.3. Neurodegeneration

Alzheimer's and Parkinson's disease have shown increases in awareness in the past quarter century. Techniques to accurately characterize disease progression and therapeutics have been topics of interest due to the increasing mortality rate [22]. qPLR has statistically validated as a trending biomarker relating to the progression of neurodegeneration, specifically for Alzheimer's disease [23]. Significant predictors of Parkinson's disease have been evaluated as well and include latency and maximum constriction velocity. Although there

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was no significant correlations drawn between disease stage and qPLR there were demonstrated correlations even in the absence of overt autonomic dysfunction [24].

8.4. Anesthesiology

The parasympathetic pathway is susceptible to depressants that can induce miosis. Miosis induction does not allow for parasympathetic relaxation to occur and therefore trends with quantity of depressant material in the brain. Oxyhemoglobin levels have been distinctly quantified to trend with the pupillary light reflex and demonstrates the recovery monitoring capability qPLR has to offer [25].



Figure 6. qPLR progression from 85% oxyhemoglobin [25]

8.5. Cognition

Cognitive load can influence the autonomic nervous system through most perception mechanisms including sound, sight, and touch. More abstractly, memory load can also play a role in cognitive effort and how this impacts the brain's latency. It has also been determined that PLR correlations to memory load diminish with age [26]. qPLR has even been proven to suffer as a result of backwards masking tasks that pull cognitive processing power away from 'wasteful' reactionary allocations [27].

9. Conclusion

qPLR has been established in recent history as a breakthrough biomarker that can reliably indi-

cate cognitive ability, injury, or neurodegradation. Reflex, as a qPLR tool, can greatly influence current trends in clinical acceptance of qPLR due to its convenience and high-accuracy. Utilization of these tools will add a significant amount of autonomic neurological data that otherwise would go unnoticed. Additionally, Reflex will take the subjectivity out of PLR analysis by providing data that is representative of the ground-truth pupillary response.

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