Towards the Development and Validation of a Smartphone-based Pupillometer for Neuro-ophthalmological Diseases Screening

Ana Isabel Sousa[1][0000−0003−2980−4742], Carlos Marques Neves[2][0000−0002−3842−2466], Luís Abegão Pinto[2][0000−0002−9960−7579], and Pedro Vieira[1][0000−0002−3823−1184]

[1] Department of Physics, Faculty of Science and Technology, NOVA University of Lisbon, Caparica Campus, 2829-516 Caparica, Portugal
[2] Faculty of Medicine, University of Lisbon, 1649-028 Lisbon, Portugal
`ai.sousa@campus.fct.unl.pt`

Abstract. Pupillometry allows a quantitative measurement of PLR and has been mainly used to assess patient's consciousness and vision function. The analysis of pupil light reflex (PLR) has been showing a renewed interest since the discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs), that are sensitive to the blue light, as they have an important role in pupil response to a stimulus. Some researches have studied pupillometry, particularly chromatic pupillometry that uses blue and red stimuli, to be a screening tool for neuro-ophthalmological diseases. Automated pupillometers have been widely used, however they are either not portable or expensive, reason why this technique has been mainly used in academic research. A smartphone-based pupillometer could be a promising equipment to overcome these limitations and to be a widespread screening tool, due to its low price, portability and accessibility. This work shows our latest advances towards the development and validation of an Android system for pupillometry measurements. Pupillometric data was collected with the smartphone application in a group of five healthy individuals and used to test our proposed data processing algorithms. These tests showed that the data processing methods that we are proposing, although promising, did not behave as expected, indicating that new approaches, better validations and corrections should be made in the future to get a stable software for pupil detection. Nevertheless, preliminary pupillometric data indicate that this system has the potential to work as an inexpensive, easy-to-use and portable pupillometer.

Keywords: Pupil · Pupillometry · Smartphone · Neuro-ophthalmology · Neuro-Ophthalmological Diseases.

1 Introduction

Pupil's main function is to control the quantity of light that enters the retina, by its constant size adjustments. [16] The way the pupil reacts to a certain stimulus is known as Pupil Light Reflex (PLR) which is regulated by the autonomic nervous system. PLR describes how the pupil rapidly constricts after a stimulus and sequentially dilates to its normal size. This response has been studied and used over the years to assess a subject's consciousness and visual system function.

Until recently, it was thought that PLR was primarily driven by rods and cones [1]. However, this perception changed with the discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs) in the early 2000's [15, 21]. These cells are a small percentage of the retinal ganglion cells (RGCs) (around 0.2% $\simeq$ 3000 cells) [5] and contain melanopsin photopigment that renders them photosensitive, particularly to the absorption of blue light [9]. Thereby, several studies [9, 25, 17, 24, 2] have shown that PLR consists in a combination of rod, cones and ipRGCs responses.

The discovery of ipRGCs in humans renewed the interest in PLR and pupillometry as it can be a non-invasive technique to assess the visual system function. With ipRGCs particularly sensitive to blue light [9] and considering that the exposure to different wavelengths stimulates differently each type of photoreceptor [3], colored stimuli started to gain interest in pupillometry. Referred as chromatic pupillometry, normally uses red or blue light stimuli, allowing the study of damages in rods, cones and ipRGCs [26]. Several studies have also shown pupillometry potential in relation to neuro-ophthalmological diseases, such as Parkinson [11, 10, 6, 31], Alzheimer [6, 13], Glaucoma [12, 5, 23, 27] or Multiple Sclerosis [4], using both chromatic or white light stimuli. Thus, pupillometry has been showing potential to be used as a screening tool for this type of diseases.

The evaluation of a subject's PLR is usually referred as pupillometry, tradicionally assessed by the clinicians with a penlight. Quantitative pupillometry, using a device normally referred as pupillometer, allows to objectively measure how pupil reacts to a certain stimulus. Since Lowenstein et al. [20] photoelectric pupillograph, several pupillometry equipments have been developed. This type of devices have evolved over the years allowing not only continuous video recording but also automatic data analysis. Pupillometers usually use infrared cameras, which give better image contrast and reduce the influence of external lights in pupil size. This characteristic is a main advantage of these pupillometers, as they allow more precise measurements of pupil size. However they are either expensive, not portable or both, which makes them hard to be widespread as a clinical tool for diseases screening and monitoring.

Smartphones interest for application in the medical field has been increasing over the years, as they have technological capabilities progressively similar to computers, are portable, accessible and have affordable prices. When compared to traditional pupillometry equipments, smartphones overcome their limitations, being a possible technology to develop a widespread tool for pupillometry.

Using a mobile phone for pupillometric measurements started in 2013 by Kim et al. [19], whose work used the smartphone camera for acquisition with an attached optical apparatus. This device had four infrared light emitting diodes (LEDs) three to improve the quality of the acquired images and a white one to work as stimulus. In this study, post processing and analysis of the acquired data was made in MATLAB$^{®}$ (Mathwords Inc., Natick, MA).

Shin et al. [28] also have used a smartphone to acquire pupillometric measurements, but instead of recording a video, this group acquired 5 steady pictures in different momentums of the experiment: before the flash, during the light stimulus and the last three after the stimulus. These images were not automatically post-processed and analyzed, instead a clinician evaluated them according to pupil size and compared the results with a penlight measurement in the same subjects and conditions. Although the smartphone usage in this case was only for the eye photographies, their results shown similar results for the smartphone application and the penlight experiment made by the clinician.

In 2018, an iPhone-based pupillometer was proposed by McAnany et al. [22], named Sensitometer, which uses the rear-facing camera and flash light to acquire a video of the pupil during constriction and redilation phases after the stimulus. This proposed system provides real time measurements of PLR, with all the acquisition and processing done in the iPhone. Results were compared with an infrared camera that was simultaneously recording pupil's response to the light stimulus and they were statistically correlated.

Recently, our team proposed an all-in-one smartphone-based pupillometer using a medium range Android device to acquire and process pupil response videos [29]. This proposed system uses the rear-facing camera and flash light of the smartphone to work as stimulus. Data processing is also performed in the smartphone, being all integrated in the same application. An algorithm for data processing was also proposed, based on Contrast Limited Adaptive Histogram Equalization (CLAHE) to increase image contrast and ElSe algorithm [7] for pupil detection. It is important to notice that the system was thought to allow chromatic pupillometry with a simple usage of a standard colored cellophane paper to work as filter to be applied in the flash light, which is relevant for neuro-ophthalmological diseases screening as previously referred.

This first proposal of the system [29] had only some preliminary results, with the application of the pupil detection algorithm to around 40 eye images, but no further testing and validation was performed. In the present work, data from 5 healthy individuals was acquired following a chromatic pupillometry protocol based in Park et al. [25] discoveries, to validate the acquisition part of the system. The data was then post-processed with the main goal to validate the algorithms proposed in [29] for pupil detection. This study also aims to understand the influence of CLAHE parameters in pupil detection by ElSe algorithm. Therefore, the data processing algorithms were applied to several frames from the videos acquired from the participant subjects. Basically, this work is a continuation of the work presented in [29] towards the validation of this smartphone-based pupillometer.

Thus, the main goal of the present work is to validate the proposed all-in-one smartphone-based pupillometer in healthy subjects. It is also intended to validate a medium range Android smartphone as a device for chromatic pupillometry allowing acquisition and running data processing algorithms.

2 Methods

This project intends to validate the low cost pupillometer system developed by our team as proposed in Sousa et al. [29]. The main goal is to use a medium range Android smartphone to acquire video of pupil response to a chromatic stimulus and post-process it to get the common parameters of PLR.

2.1 Study Participants

Five participants with no known visual abnormalities have been selected. All participants underwent a standard ophthalmic screening test to measure vision acuity, by autorefractor and Early Treatment Diabetic Retinopathy Study (ETDRS) 2 meters exams, and intraocular pressure (IOP).

Pupillometry measurements were only made in the left eye in each subject, for the different conditions and types of experiments. All the recorded videos and participants data was anonymized and codified.

This study was approved by the Hospital Santa Maria ethics committee, and a written informed consent was obtained from all the individual participants.

2.2 Pupillometry System

The main goal of the proposed system is to use a medium range Android smartphone to allow acquisition and processing of pupillometric data, without the need of other equipments. For this purpose an Android application was developed that could support the desired functions. The device used in this study is a Nokia 7 Plus (Nokia Corporation, HMD Global, Finland), with Android operation system, version 9 Pie. This smartphone has front and two rear facing cameras but for this study only rear facing cameras were used, particularly due to the flash light that is linked to them, needed for light stimulus.

This system, summarized in Figure 1, has two main sections: acquisition and data processing. As an all-in-one system, it contemplates different programming languages working together such as Java and C++, that communicate through Java Native Interface (JNI) framework which enables the integration of C or C++ code in Java Android application.

The acquisition part is mainly formed by the smartphone camera, the flash light and the application that controls their functioning. To do so, the Camera2 API is the Android interface used that allows proper control of smartphone cameras and flash and adjustment of the recording characteristics. The application that was developed for this system access the rear-facing cameras, starts recording, flashes a light stimuli automatically at a certain instant and stores the recorded video for post-processing. Recording duration and flash instant are parameters configurable in the application, allowing different experiments in terms of acquisition protocol.

The rear-facing flash allows a white light stimuli, however chromatic pupillometry is desired in this system to assess the influences of rods, cones and ipRGCs in pupil light reflex, as previously mentioned. To achieve this chromatic

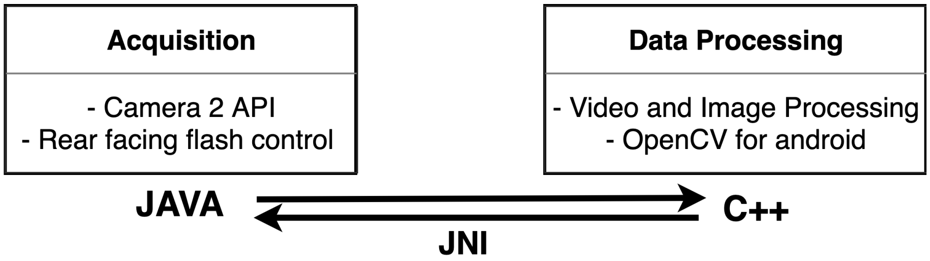


Fig. 1: Proposed system architecture, adapted from [29].

light stimuli, a standard grade cellophane paper is used as filter in front of the flash light, in both blue and red colors. Flash spectrum was acquired with a spectrometer in previous work, as referred in [29], indicating that these filters should be enough to get the desired light wavelengths in blue and red spectra.

2.3 Data Processing

The second main section of this system is the data processing, that allows data extraction of the pupil videos. This process was developed using OpenCV for image processing, in both Java and C++, integrated in the Android application developed by the team. In this case, video processing is composed by getting all the frames, in each frame get the eye region and apply a pupil detection algorithm that will return its location and size. Having the pupil properly detected allows to build a graphic of the variation of the pupil size through time for a given experiment, which is used to understand PLR and compare between different experiments and protocols.

To detect the eye in each frame, OpenCV Haar-cascade eye detector, based in Viola and Jones Haar-cascade object detection algorithm [30], was used to reduce the area for pupil detection. The detected region area was verified and the regions with an area smaller area were automatically discarded, due to the cases where Haar-cascade algorithm fails to detect the eye.

Pupil detection in each eye frame is then the next data processing step. Each eye cropped image is converted to gray scale and image processing algorithms are applied to achieve the desired pupil detection. In [29] our team have proposed the application of Contrast Limited Adaptive Histogram Equalization (CLAHE) and then ElSe algorithm, developed by Fuhl. et al [7] for pupil detection is real world scenarios. A summary of this process is shown in Figure 2.

Even though in our previous work [29] CLAHE didn't seem to make a difference in the pupil detection, as the results were similar to the images without any CLAHE application, the dataset used was small to take that conclusion. Therefore, we have tested again the influence of CLAHE in pupil detection in our system. With the goal to enhance image contrast, CLAHE is used as a way to overcome the low contrast between iris and pupil in images acquired by non-infrared cameras, such as the smartphone one. This method overcome simple

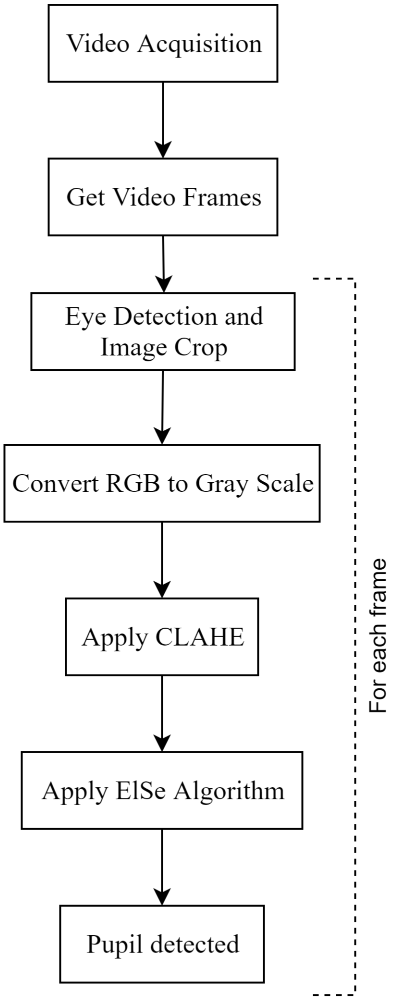


Fig. 2: Data processing algorithms flowchart, as referred in [29].

histogram equalization or adaptive histogram equalization for iris recognition in Hassan et al. study [14]. OpenCV CLAHE function has two main parameters, the clipLimit, that represents the threshold from which the histogram is clipped and redistributed, and the tileGridSize, related to the tile size that the input will be sliced for the algorithm application. In the present work these two parameters of CLAHE were tested in order to better understand how this value influences the pupil detection in the videos acquired with our system. Tests were made with OpenCV CLAHE function default values, clipLimit = 4.0 and tileGridSize = (8,8), and clipLimit = 10.0 and tileGridSize = (10,10), that leads to a higher increase of the contrast in the images. This tests were made in 1071 eye frames acquired from different individuals.

After image enhancement, pupil detection is the main concern in this process. Although it is an apparently easy task, as the pupil is the black round area of the image, some difficulties need to be overcome such as low contrast between pupil and iris, blur, reflexes, illumination issues and other scenarios. Many algorithms have been developed over the years to achieve a proper pupil detection and ElSe algorithm, by Fuhl et al. [7], was considered the gold standard [8]. ElSe, that stands for Ellipse Selection, is an open source algorithm developed in C# that was targeted and tested in images acquired with infrared cameras in real world scenarios. As the name implies, this algorithm tries to find in a gray scale image the best suitable ellipse that could be the pupil. Very briefly, ElSe starts with the application of a Canny filter to get the image edges which are then filtered with straightening patterns. After this morphological operations, the straight lines are discarded and least square ellipse fitting is applied to get the best ellipse, after an ellipse evaluation to exclude unlikely pupils. If this process fails, a second approach is tried through a coarse positioning of the pupil. Image is downscaled and a convolution is applied with a surface and a mean filters. After multiplying the results of the convolutions, the resultant maximum value is defined as the starting point to be refined. This point surroundings are verified and the center of mass of the pixels under this threshold is the new pupil position. ElSe algorithm was tested in datasets acquired with infrared cameras, which is slightly different from the images acquired with a smartphone camera.

After pupil detection in each frame, pupil size variation through time should be normalized by the baseline, correspondent to the mean pupil size before the light stimulus. Pupil normalization was made based in the equation mentioned in [18], adapted for both pupil diameter or area variations, where 100% means pupil in its baseline size:

$$\text{pupil constriction} = 100 - \frac{\text{pupil baseline size} - \text{absolute pupil size}}{\text{pupil baseline size}} \times 100 \quad (1)$$

2.4 Chromatic Pupillometry Protocol and Preliminary Experiments

A pupillometry experiment needs to take into account a period for the pupil adaptation to the ambient light conditions, to get a proper measurement of PLR to the light stimulus, then recording should start for a short duration to get pupil size baseline, then a short colored light stimulus followed by a post-stimulus period after which the recording stops. In the present work a protocol for chromatic pupillometry is proposed, considering these intervals and based on the literature. Adapted from Park et al. [25] proposed pupillometry protocol, our protocol, showed in Figure 3, records the pupil for 5 seconds, then flashes the light stimulus, with 1 second duration, and continues recording for 30 seconds to get the pupil redilation phase. In the beginning of the experiment subjects were 7 minutes in the light ambient conditions, which in this case was a mesopic environment, to pupil adaptation. There was 5 minute pause without recording, in the same light conditions, between experiments. This chromatic pupillometry protocol was applied in each participant, first for red light stimulus followed by the blue stimulus.

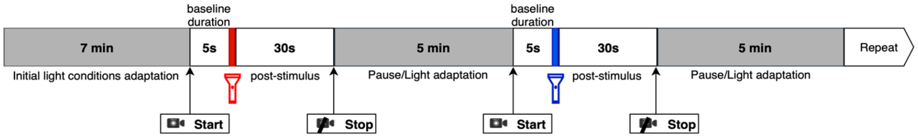


Fig. 3: Proposed protocol for chromatic pupillometry. Schema adapted from [29].

The smartphone was fixed in a support in front of subject's face, which was resting in a face support common in ophthalmology equipments. The apparatus is shown in Figure 4. During the acquisition time, subject's were focusing their vision in the center of an image usually used in autorefractors to avoid accommodation. In this way, the individuals eyes were focusing in that point, without moving all around, and the proximity of the smartphone to their face's and eye sight was overcome.

Fig. 4: Apparatus used to fix the smartphone in front of individual's face and to have a controlled ambient light.

To each recorded video the data processing algorithm was applied in order to evaluate its efficiency in videos acquired with this proposed pupillometric system and in the light conditions they were acquired.

3 Results and Discussion

3.1 Study Participants

Five participants were included in this study, their demographic and ophthalmic characteristics are shown in Table 1. This group has an average age of 19.8, in a range of 18 to 23 years old. They present no known vision abnormalities or other kind of diseases, meaning it is considered a healthy group of participants. They were all cooperative and felt no discomfort during the experiments.

Table 1: Demographic characteristics of study participants

Characteristics	**Healthy participants data**
Age	19.8 ± 2
Gender (F:M)	4:1
IOP (left eye)	13.9 ± 4.9

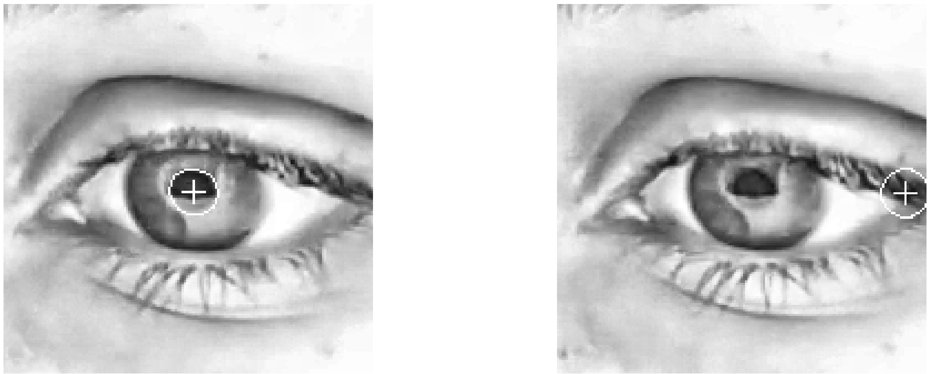
3.2 Data Processing Results and Discussion

The first validation of this system was in the acquisition part, with the proper working of the smartphone application during the recording period in the five participants. The application performed as expected, automatically applying the flash light at the desired instant and stopping the record 30 seconds after that. Each video was stored in the smartphone for post processing.

Video data processing was made as suggested in the flowchart presented in Figure 2, testing different values of CLAHE, as referred in Section 2.3.

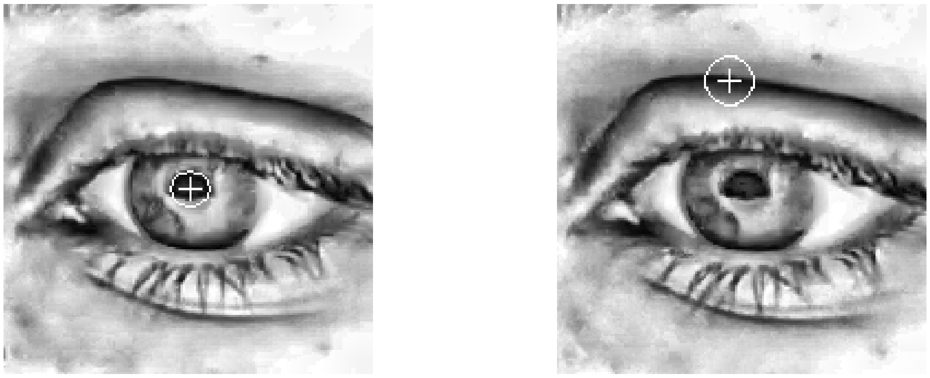
To test the detection algorithm and the influence of CLAHE parameters, 1071 frames from different subjects were analyzed with both default values (clipLimit = 4.0 and tileGridSize = (8,8)) and clipLimit = 10.0 and tileGridSize = (10,10). Some examples of images with successful and failed detection for both default values and 10.0 for CLAHE parameters are shown in Figures 5 and 6, respectively. Pupil detection was manually verified. It is considered a success, cases in which the algorithm finds the center and the contours of the pupil correctly. A summary of number of successes and failures in the tested eye images is presented in Table 2.

In 1071 eye images tested, the algorithm had low success, being the error 88.4% for default CLAHE parameters and 93.6% for the others. This results were really low and not as expected. Although considering that ElSe algorithm [7] was tested in images acquired with infrared cameras, as the algorithm was developed for real world scenarios we were expecting better results, as the testing dataset of Fuhl et al. [7] had several images with poor quality, many reflexes and glares. However just applying CLAHE for image enhancement and then ElSe algorithm does not seem to be enough for our system.



(a) Successful pupil detection. (b) Failed pupil detection.

Fig. 5: Examples of detection in images with default (clipLimit = 4.0 and tileGridSize = (8,8)) CLAHE parameters.



(a) Successful pupil detection. (b) Failed pupil detection.

Fig. 6: Examples of detection in images with clipLimit = 10.0 and tileGridSize = (10,10) CLAHE parameters.

Table 2: Results of variation in CLAHE parameters in pupil detection

cutLimit	tileGridSize	Frames with success	Frames failed
4.0	(8,8)	124 = 11.6%	947 = 88.4%
10.0	(10,10)	69 = 6.4%	1002 = 93.6%
	Total frames	1071	1071

3.3 Preliminary Pupillometry Results

As observed in last section 3.2, the algorithm for pupil detection that our team proposed in [29] is not working in all frames and does not present enough stability for the acquisitions made with the participants. As the algorithms did not perform as expected, difficulties in constructing a PLR graphic, with pupil size variation in function of time, were suffered.

Nevertheless, with the goal and effort to see the typical pupillometry curve, the video of one of the participants in the case of a blue stimulus was used for some other try. After some enhancement of the results, we tried to filter some wrong measurements, for example, if the center of the pupil was much deviated from the previous one or the pupil didn't have a circular shape values were discarded. A median filter and a smoothing were applied. After doing this, the results were plotted in function of time and we obtained a graphic like the one shown in Figure 7.

Even though the noticeable imperfections in the resultant graph and a decay in the pupil size between 15 and 25 seconds that is abnormal in a healthy patient and must be related to errors in pupil detection, one can see the expected PLR behavior: fast pupil constriction after the light stimulus until around half the size and a redilation after that. This constriction until around 50% of the baseline is concordant with what Park et al. [25] show in their study for 1 second flash stimulus for a healthy individual.

Despite the clear need for improvements in terms of data processing and pupil detection, it is visible that this system is in the right track to be a pupillometer tool. This preliminary pupillometric results showed that the the rear-facing flash of the smartphone is capable enough of causing pupil reaction and the Nokia 7 Plus camera has enough quality for the acquisition process.

4 Conclusion

The possibilities of applications and usage for smartphones in the medical field are huge, due to their low price, easy access, portability and being used by everyone all over the world. This are great advantage in terms of pupillometry, that could allow to have a widespread screening and monitoring tool in diseases such as Parkinson's, Glaucoma or Alzheimer's, as previously mentioned.

Although there are some studies using a smartphone for pupillometry measurements, the system we proposed, first mentioned in [29] and the target of the present work, uses a medium range Android device and allows chromatic

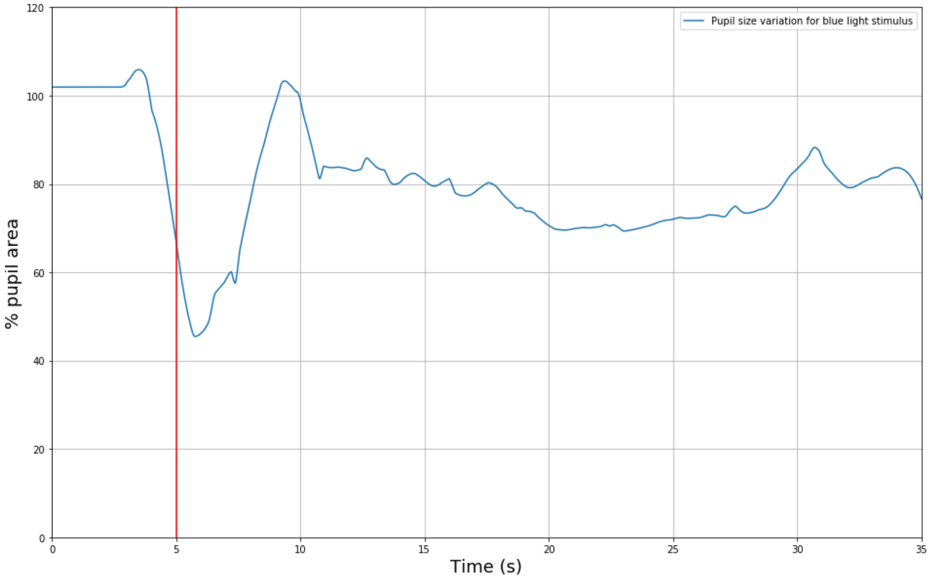


Fig. 7: Graphic showing some preliminary filtered results for one of the participants in the case of blue light stimulus. The vertical red line represents the flash instant.

pupillometry which is necessary for diseases screening due to different color sensitivities of rods, cones and ipRGCs. We were able to prove functioning of the acquisition part of the system, showing that the Nokia 7 Plus flash light and camera are a sufficient equipment for pupillometric measurements. As for the data processing stage of the system, we are not yet with a stable and efficient method, particularly in the pupil detection part of the algorithm. There is a need to improve the algorithm that was proposed in [29] and further explored in this work, to define validations to automatically verify if the pupil was properly detected and possibly to develop alternative algorithms in case it fails.

The data acquired in this experiment allowed to have a proper knowledge of the acquired videos quality, the possible existant reflexes in each frame, as the smartphone is in front of subject's face and reflects in the eye, and other constraints. It also will allow the team to continue developing and improving the algorithms for pupil detection, clearly needed to properly validate the system as a whole.

Further work is then to improve the algorithms of pupil detection, so that this system can be prepared to severe illumination conditions and reflexes in the pupil. It is also important to make tests in different ambient light conditions to validate the algorithms and the system as a whole so that it can be used in different scenarios.

Finally, after the enhancement in data processing system and to proper validate the protocol in healthy individuals, the next steps include the validation of this smartphone-based pupillometer in patients with neuro-ophthalmological diseases. The main interest is to validate that this is an interesting and potential tool for early screening pathologies such as Parkinson's, Alzheimer's or Glaucoma.

Despite the need of improvements and more validation, the present work added some validation steps needed to show the potential of the proposed system. Smartphones seem to be promising devices for pupillometry, particularly to take this technique more close to clinical application, to be used as a screening tool for neuro-ophthalmological diseases.

5 Acknowledgments

This work is funded by National Funds through FCT - Portuguese Foundation for Science and Technology and Compta S.A. under the PhD grant with reference PD/BDE/135002/2017. A special acknowledgment to Compta S.A. team and to the Ophthalmology Department of Hospital Santa Maria for all the support given.

References

1. Alpern, M., Campbell, F.W.: The spectral sensitivity of the consensual light reflex. The Journal of Physiology **164**(3), 478–507 (1962). https://doi.org/10.1113/jphysiol.1962.sp007033
2. Barrionuevo, P.A., Nicandro, N., McAnany, J.J., Zele, A.J., Gamlin, P., Cao, D.: Assessing rod, cone, and melanopsin contributions to human pupil flicker responses. Investigative Ophthalmology and Visual Science (2014). https://doi.org/10.1167/iovs.13-13252
3. Dacey, D.M., Liao, H.W., Peterson, B.B., Robinson, F.R., Smith, V.C., Pokomy, J., Yau, K.W., Gamlin, P.D.: Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. Nature (2005). https://doi.org/10.1038/nature03387
4. de Rodez Benavent, S.A., Nygaard, G.O., Harbo, H.F., Tønnesen, S., Sowa, P., Landrø, N.I., Wendel-Haga, M., Etholm, L., Nilsen, K.B., Drolsum, L., Kerty, E., Celius, E.G., Laeng, B.: Fatigue and cognition: Pupillary responses to problem-solving in early multiple sclerosis patients. Brain and Behavior **7**(7), 1–12 (2017). https://doi.org/10.1002/brb3.717
5. Feigl, B., Mattes, D., Thomas, R., Zele, A.J.: Intrinsically Photosensitive (Melanopsin) Retinal Ganglion Cell Function in Glaucoma pp. 4362–4367 (2011). https://doi.org/10.1167/iovs.10-7069
6. Fotiou, D.F., Stergiou, V., Tsiptsios, D., Lithari, C., Nakou, M., Karlovasitou, A.: Cholinergic deficiency in Alzheimer's and Parkinson's disease: Evaluation with pupillometry. International Journal of Psychophysiology **73**(2), 143–149 (2009). https://doi.org/10.1016/j.ijpsycho.2009.01.011, http://dx.doi.org/10.1016/j.ijpsycho.2009.01.011
7. Fuhl, W., Santini, T.C., Kuebler, T., Kasneci, E.: ElSe: Ellipse Selection for Robust Pupil Detection in Real-World Environments (2015). https://doi.org/10.1145/2857491.2857505, http://arxiv.org/abs/1511.06575

8. Fuhl, W., Tonsen, M., Bulling, A., Kasneci, E.: Pupil detection for head-mounted eye tracking in the wild: an evaluation of the state of the art. Machine Vision and Applications **27**(8), 1275–1288 (nov 2016). https://doi.org/10.1007/s00138-016-0776-4, http://arxiv.org/abs/1405.0006 http://link.springer.com/10.1007/s00138-016-0776-4
9. Gamlin, P.D., McDougal, D.H., Pokorny, J., Smith, V.C., Yau, K.W., Dacey, D.M.: Human and macaque pupil responses driven by melanopsin-containing retinal ganglion cells. Vision Research **47**(7), 946–954 (2007). https://doi.org/10.1016/j.visres.2006.12.015
10. Giza, E., Fotiou, D., Bostantjopoulou, S., Katsarou, Z., Gerasimou, G., Gotzamani-Psarrakou, A., Karlovasitou, A.: Pupillometry and 123I-DaTSCAN imaging in Parkinson's disease: A comparison study. International Journal of Neuroscience **122**(1), 26–34 (2012). https://doi.org/10.3109/00207454.2011.619285
11. Giza, E., Fotiou, D., Bostantjopoulou, S., Katsarou, Z., Karlovasitou, A.: Pupil Light Reflex in Parkinson's Disease: Evaluation With Pupillometry. International Journal of Neuroscience **121**(1), 37–43 (jan 2011). https://doi.org/10.3109/00207454.2010.526730, http://www.tandfonline.com/doi/full/10.3109/00207454.2010.526730
12. Gracitelli, C.P.B., Duque-Chica, G.L., Moura, A.L., Nagy, B.V., de Melo, G.R., Roizenblatt, M., Borba, P.D., Teixeira, S.H., Ventura, D.F., Paranhos, A.: A Positive Association Between Intrinsically Photosensitive Retinal Ganglion Cells and Retinal Nerve Fiber Layer Thinning in Glaucoma. Investigative Ophthalmology & Visual Science **55**(12), 7997–8005 (2014). https://doi.org/10.1167/iovs.14-15146
13. Granholm, E.L., Panizzon, M.S., Elman, J.A., Jak, A.J., Hauger, R.L., Bondi, M.W., Lyons, M.J., Franz, C.E., Kremen, W.S.: Pupillary Responses as a Biomarker of Early Risk for Alzheimer's Disease. Journal of Alzheimer's Disease **56**(4), 1419–1428 (feb 2017). https://doi.org/10.3233/JAD-161078, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5808562/
14. Hassan, R., Kasim, S., Jafery, W.A.Z.W.C., Shah, Z.A.: Image enhancement technique at different distance for Iris recognition. International Journal on Advanced Science, Engineering and Information Technology **7**(4-2 Special Issue), 1510–1515 (2017)
15. Hattar, S., Liao, H.W., Takao, M., Berson, D.M., Yau, K.W.: Melanopsin-containing retinal ganglion cells: Architecture, projections, and intrinsic photosensitivity. Science **295**(5557), 1065–1070 (2002). https://doi.org/10.1126/science.1069609
16. Kardon, R.: Regulation of Light through the Pupil. In: Kaufman, P.L., Alm, A. (eds.) Adler's Physiology of the eye, chap. 26, pp. 502–525. Elsevier, St Louis: Mosby, 11th ed. edn. (2011)
17. Kardon, R., Anderson, S.C., Damarjian, T.G., Grace, E.M., Stone, E., Kawasaki, A.: Chromatic Pupil Responses. Preferential Activation of the Melanopsin-mediated versus Outer Photoreceptor-mediated Pupil Light Reflex. Ophthalmology **116**(8), 1564–1573 (2009). https://doi.org/10.1016/j.ophtha.2009.02.007, http://dx.doi.org/10.1016/j.ophtha.2009.02.007
18. Kelbsch, C., Strasser, T., Chen, Y., Feigl, B., Gamlin, P.D., Kardon, R., Peters, T., Roecklein, K.A., Steinhauer, S.R., Szabadi, E., Zele, A.J., Wilhelm, H., Wilhelm, B.J.: Standards in Pupillography. Frontiers in Neurology **10** (feb 2019). https://doi.org/10.3389/fneur.2019.00129, https://www.frontiersin.org/article/10.3389/fneur.2019.00129/full

19. Kim, T.H., Youn, J.I.: Development of a smartphone-based pupillometer. Journal of the Optical Society of Korea **17**(3), 249–254 (2013). https://doi.org/10.3807/JOSK.2013.17.3.249
20. Lowenstein, O., Loewenfel, I.E.: Electronic Pupillography; A New Instrument and Some Clinical Applications. A.M.A. Archives of Ophthalmology **59**(3), 352 (mar 1958). https://doi.org/10.1001/archopht.1958.00940040058007
21. Lucas, R.J., Douglas, R.H., Foster, R.G.: Characterization of an ocular photopigment capable of driving pupillary constriction in mice. Nature Neuroscience **4**(6), 621–626 (2001)
22. McAnany, J.J., Smith, B.M., Garland, A., Kagen, S.L.: IPhone-based pupillometry: A novel approach for assessing the pupillary light reflex. Optometry and Vision Science **95**(10), 953–958 (2018). https://doi.org/10.1097/OPX.0000000000001289, http://insights.ovid.com/crossref?an=00006324-201810000-00007
23. Najjar, R.P., Sharma, S., Atalay, E., Rukmini, A.V., Sun, C., Lock, J.Z., Baskaran, M., Perera, S.A., Husain, R., Lamoureux, E., Gooley, J.J., Aung, T., Milea, D.: Pupillary Responses to Full-Field Chromatic Stimuli Are Reduced in Patients with Early-Stage Primary Open-Angle Glaucoma. Ophthalmology **125**(9), 1362–1371 (2018). https://doi.org/10.1016/j.ophtha.2018.02.024, https://doi.org/10.1016/j.ophtha.2018.02.024
24. Park, J.C., McAnany, J.J.: Effect of stimulus size and luminance on the rod-, cone-, and melanopsin-mediated pupillary light reflex. Journal of Vision **15**(3), 1–13 (2015). https://doi.org/10.1167/15.3.13
25. Park, J.C., Moura, A.L., Raza, A.S., Rhee, D.W., Kardon, R.H., Hood, D.C.: Toward a Clinical Protocol for Assessing Rod, Cone, and Melanopsin Contributions to the Human Pupil Response. Investigative Opthalmology & Visual Science **52**(9), 6624 (aug 2011). https://doi.org/10.1167/iovs.11-7586
26. Rukmini, A.V., Milea, D., Gooley, J.J.: Chromatic pupillometry methods for assessing photoreceptor health in retinal and optic nerve diseases. Frontiers in Neurology **10**(FEB), 1–20 (2019). https://doi.org/10.3389/fneur.2019.00076
27. Rukmini, A.V., Milea, D., Baskaran, M., How, A.C., Perera, S.A., Aung, T., Gooley, J.J.: Pupillary Responses to High-Irradiance Blue Light Correlate with Glaucoma Severity. Ophthalmology **122**(9), 1777–1785 (2015). https://doi.org/10.1016/j.ophtha.2015.06.002, http://dx.doi.org/10.1016/j.ophtha.2015.06.002
28. Shin, Y.D., Bae, J.H., Kwon, E.J., Kim, H.T., Lee, T.S., Choi, Y.J.: Assessment of pupillary light reflex using a smartphone application. Experimental and Therapeutic Medicine **12**(2), 720–724 (aug 2016). https://doi.org/10.3892/etm.2016.3379, https://www.spandidos-publications.com/10.3892/etm.2016.3379
29. Sousa, A.I., Almeida, R.V., Narciso, M., Crivellaro, F.S., Neves, C.M., Pinto, L.A., Vieira, P.: Development of a smartphone-based pupillometer for neuro-ophthalmological diseases screening. BIODEVICES 2020 - 13th International Conference on Biomedical Electronics and Devices, Proceedings; Part of 13th International Joint Conference on Biomedical Engineering Systems and Technologies, BIOSTEC 2020 (Biostec), 50–56 (2020). https://doi.org/10.5220/0008962600500056
30. Viola, P., Jones, M.: Rapid object detection using a boosted cascade of simple features. In: Proceedings of the 2001 IEEE Computer Society Conference on Computer Vision and Pattern Recognition. CVPR 2001. vol. 1, pp. I–511–I–518. IEEE Comput. Soc (2001). https://doi.org/10.1109/CVPR.2001.990517, http://ieeexplore.ieee.org/document/990517/

31. Wang, C.A., McInnis, H., Brien, D.C., Pari, G., Munoz, D.P.: Disruption of pupil size modulation correlates with voluntary motor preparation deficits in Parkinson's disease. Neuropsychologia **80**, 176–184 (jan 2016). https://doi.org/10.1016/j.neuropsychologia.2015.11.019, http://dx.doi.org/10.1016/j.neuropsychologia.2015.11.019 https://linkinghub.elsevier.com/retrieve/pii/S0028393215302347