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# Pupillary light reflex as a diagnostic aid from computational viewpoint: A systematic literature review

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ABSTRACT

This work presents a detailed and complete review of publications on pupillary light reflex (PLR) used to aid diagnoses. These are computational techniques used in the evaluation of pupillometry, as well as their application in computer-aided diagnoses (CAD) of pathologies or physiological conditions that can be studied by observing the movements of miosis and mydriasis of the human pupil. A careful survey was carried out of all studies published over the last 10 years which investigated, electronic devices, recording protocols, image treatment, computational algorithms and the pathologies related to PLR. We present the frontier of existing knowledge regarding methods and techniques used in this field of knowledge, which has been expanding due to the possibility of performing diagnoses with high precision, at a low cost and with a non-invasive method.

## 1. Introduction

Over the last decades, pupillometry has been useful to health professionals. Initially, the method was limited to the use of a flashlight aimed at the pupil to assess impairment of consciousness [1,2]. Advances in technology and the development of devices capable of accurately measuring the diameter of the pupil have enabled more sophisticated and accurate assessments. Currently, studies show that pupillary reaction to light can help specialists perform different types of diagnoses.

Diagnosis is the analytical process of examining clinical images to reach a conclusion. This analysis is often supported by exams. These can be images or even the evaluation of metadata generated from laboratory evaluations. As examples, we can mention blood counts, electrocardiograms, retinal exam images and several others. Based on these tests, specialists perform the diagnosis and determine the patient's health or physiological condition.

A computer-aided detection and diagnosis system (Computer-Aided Detection and Diagnosis - CAD) is a class of computer systems whose objective is to help find and diagnose diseases and provide a "second opinion" in the interpretation of exams [3]. The goal of CAD systems is to improve the hit rates of experts and reduce the time required for image interpretation [4]. In this sense, automated pupillometry is a CAD system used for pupil images that can help diagnose pathologies, physiological conditions, and cognitive or emotional status. It also allows the assessment of interest, effort in decision-making, tiredness, fatigue, drug use, and functions of the autonomic system. The practicality and assertiveness of pupillometry has roused the interest of the research community, and thus, a considerable amount of research has been published in recent years to aid diagnostics (see Fig. 1).

This growing amount of research and the improvement of techniques to perform pupillometry raise some important questions from a computational point of view about the techniques addressed in the studies, namely:

**Q1:** What devices are used to acquire images when performing pupillometry?
**Q2:** What is the protocol applied in carrying out the study?
**Q3:** What are the methods used to measure pupillary diameter (pupillary detection and segmentation)?
**Q4:** What techniques are used to treat noise and other artifacts such as blinks?
**Q5:** In which pathology diagnoses has pupillometry been applied?
**Q6:** What is the accuracy rate of the research regarding precision in aiding diagnosis?
**Q7:** Which Artificial Intelligence (AI) techniques have been applied and what results have been obtained?

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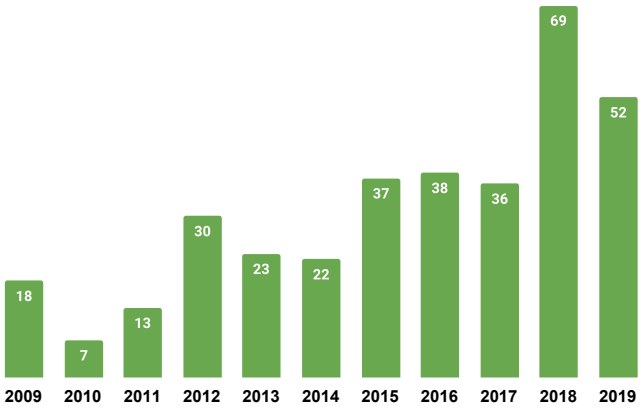



**Fig. 1.** Number of papers per year, which used PLR to aid diagnosis.

To reproducibly consolidate what is available in the literature, systematic review techniques were used. Systematic literature review (SLR) aims to identify, select, evaluate, interpret and summarize available studies considered relevant to a research topic [5].

This review lists computational techniques employed in automated pupillometry recurring in the scientific literature. It summarizes the techniques used to help identify pathologies and physiological conditions related to pupillary light reflex. It also point out directions for new research aimed use PLR in aiding diagnostics.

## 2. Material and methods

### 2.1. Planning

The methodology used in this review was proposed by Kitchenham [5], which considers planning, conducting and reporting as the main stages of building an SLR.

In the planning phase, articles previously classified as relevant were used to carry out exploratory searches and support the definition of the search criteria. In this stage, it was defined that:

- The literature search would be done in the ACM Library (https://dl.acm.org/search/advanced); IEEE Explorer (https://ieeexplore.ieee.org/search/advanced); Science Direct (https://www.sciencedirect.com/search/advanced) and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/advanced) databases.
- The research considered in this review would be from 2009 to 2019 for a full ten-year cycle of publications.
- To be considered for inclusion in this SRL, the studies should be original, and performed on humans, who used automated pupillometry to evaluate PLR. Also included were studies that sought to address challenges that pupillometry needed to overcome in order to be useful in assisting diagnoses (e. g. capture devices, processing of captured images and classification).
- Incomplete studies, written in a language other than English, unavailable on the internet or that had not been peer-reviewed were considered unsuitable for this SLR.
- The keywords were: “pupil”, “pupillometry”, “pupillometer”, “pupillary”, “pupillometric”, “pupillography”; connected with “OR”, and the keywords “teacher” and “school” connected with “NOT”. The search string was “pupil OR pupillometry OR pupillometer OR pupillary OR pupillometric OR pupillography NOT teacher NOT school”. This was applied to metadata: title, abstract, and keywords of author(s).

### 2.2. Selection

The primary searches were carried out in July 2020 and returned 5547 papers, 452 from the ACM Library, 1025 from the IEEE, 2112 from PubMed and 1958 from ScienceDirect (Fig. 2), which resulted in 5188 references after the removal of duplicates.

The independent evaluators (H.P and R.C), after reading the title and summary of the articles, considered 367 pertinent to human pupillary behavior. These articles were then evaluated using the following exclusion criteria: (I) using light stimulation of the pupil (exclusively or in conjunction with other stimuli) to assist in diagnoses, (II) establishing reference values for pupil behavior, (III) improving technical aspects to pupillometry (e.g. developing recording device, developing pupil detection and segmentation algorithms, developing techniques to detect blinks or to remove artifacts). The application of these exclusion criteria resulted in 345 articles selected for complete reading and the extraction of information. Of these papers, 174 used pupillary reflex to light to assist diagnoses, and 171 established reference values for pupillary behavior, or developed recording devices, or segmentation protocol, or pupil detection algorithms, or made revisions on these subjects.

## 3. Report review

Pupillary movements result from the balance between the activity of the sphincter muscle of the iris innervated by the parasympathetic nervous system (PNS) responsible for pupillary contraction and the activity of the dilator muscle of the iris innervated by the sympathetic nervous system (SNP) [6,7]. The pupillary response to light is measured by intrinsically photosensitive melanopsin-containing retinal ganglion cells (ipRGCs) that receive stimuli from the Rod and Cone photoreceptors [8].

Clinical diagnosis of physiological or pathological conditions that alter the interaction between sympathetic dilation and parasympathetic constriction, affect neurotransmitter circuits or modify the dynamics of pupillary behavior may, hypothetically, be aided by dynamic pupillometry.

Pupillometry is the measurement of the pupillary diameter and can be performed in a static or dynamic way. Static pupillometry is performed by measuring the pupillary diameter at a given time. Dynamic pupilometry is performed by measuring the pupil diameter continuously during a certain period. Pupilometry is usually performed under constant light conditions, which can be: low (scotopic), medium (mesopic) or high (photopic).

The devices used to perform the pupillometry range from a flashlight (*swinging flashlight test*) to, pupillometers and eye trackers (*eye trackers*) that perform pupillometry in an automated way.

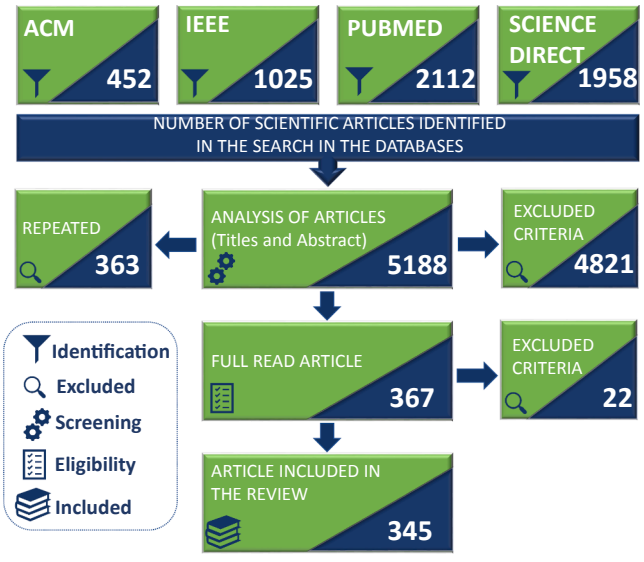



**Fig. 2.** The systematic review process.

### 3.1. Device for recording pupillary behavior - pupillometer

The manual (visual) measurement of pupillary behavior has been shown to be inaccurate and inadequate for analyzes that go beyond checking the state of coma or whether the person is alive. Since the 1950s, equipment has been developed and improved to accurately measure the pupillary diameter [9]. Several models of commercial pupillometers are currently available.

Among commercial pupilometers, the most frequently used to aid diagnosis were NeurOptics pupilometers (20% of articles), especially the NeurOptics NPi-200 model (NeurOptics Inc., Irvine CA USA) used in 20 studies. The second most used were the RAPDx (Konan Medical USA, Irvine, California, USA), used in 15 studies (13%), the ViewPoint Eye-Tracker (Arrington Research, Scottsdale, AZ) used in 14 surveys (12%) and the Compact Integrated Pupillograph (CIP; AMTech, Dossenheim, Germany) in 12 (10%). These four commercial pupilometers together represent more than half of all the studies that opted for commercial devices (52%). Below is a brief description of these devices.

NeurOptics NPi-200 works with infrared images. Pupillary stimulation is performed with white light applied with configurable duration and intensity. It has been widely used in the measurement of pupillary reactivity in critically ill patients with advanced brain injuries, as it provides the automatic calculation of NPi (pupillary neurological index). This index is a scalar value that varies from 0 to 5; values greater than 3 indicate normal behavior, lower values suggest a prognosis of brain injury. This index is calculated by comparing the amplitude and speed of the pupillary reflex with the reference values [10].

In the 20 articles where this device was used, dynamic pupillometry was applied to identify brain injuries, obtain reference values, post-stroke prognosis, to detect asthma, delirium, optic neuritis, and Horner's syndrome, and to identify drug use. Among the articles that used this device, only Yung Ju Yoo et al. [11] presented the sensitivity and specificity values in identifying Horner's syndrome, 84.6% and 92.3%, respectively.

The RAPDx device operates with infrared images. Pupils can be stimulated with white or multi-chromatic light. Unlike NeurOptics, in order to capture images, a person needs to approach the face of a cyclops-shaped device that partially isolates external lighting. Images and stimuli can be acquired independently for each eye. There is also the possibility of connecting the device to a computer network and cloud services.

This device was used in 15 articles that evaluated glaucoma, DPAR, amblyopia, age-related macular degeneration and to obtain reference values. Among all the articles examined, the best accuracy was presented by Dolly S Chang et al. [12], who obtained 80% sensitivity and specificity in identifying glaucoma.

The ViewPoint EyeTrackers device is used in for *eye-tracking* activities. Images are acquired with two cameras coupled to a support for the person's face. This device does not isolate external lighting and does not have a lighting/ stimulation system for the pupil of the person being recorded. It was used in 14 articles that aimed to identify glaucoma, diabetes, optic neuritis, idiopathic intracranial hypertension, sleep or fatigue, obstructive sleep apnea and to obtain reference values.

Jason C Park et al. [13] presented sensitivity and specificity values of 85% in the identification of idiopathic intracranial hypertension. Not all other articles showed accuracy, sensitivity or specificity.

Similar to the ViewPoint EyeTrackers, the Compact Integrated Pupillograph device that was used in 12 articles does not have external lighting isolation. However, it does have a pupil lighting/ stimulation system. It is also a camera system with a support where the person approaches the face to have the images of the eyes captured.

The device was used in articles that sought to identify alcohol withdrawal, Alzheimer's, migraines, heart rates, hemianopsia, retinitis pigmentosa, sleep or fatigue. However, none of the articles show accuracy, sensitivity or specificity.

These four commercial devices have been the most used in research in the past 10 years. In addition to these, there are other pupillometers. Most of the studies used commercial devices, due to practicality, precision and available resources. However, some studies, whether due to cost or configuration flexibility, preferred to develop their own customized devices. Some commercial devices, including the four already described, are shown in the Table 1 ordered from most to least used. Altogether, 115 articles used commercial devices, for a total of 15 commercial devices.

### 3.2. Pupil stimulation and recording protocol

Recording protocol, in the context of pupillometry with light stimulation, concerns how the photoreceptor cells will be stimulated. It defines which wavelength of light (*waveform*) will be used, which is the intensity of the stimulus, the duration of the stimulus, the number of times a person will be tested, the period of adaptation to light (initial and between stimulus) and finally what kind of reflex will be used: direct, when the stimulated eye is also filmed, or consensual when one eye is stimulated and the other is filmed.

Rod cells, cone cells and intrinsically photosensitive retinal ganglion cells (ipRGCs) are photoreceptor cells that induce PLR. Rod cells are responsible for vision in the dark (scotopic vision). Cone cells are color sensitive and responsible for vision in a bright environment (photopic vision). Both are involved in intermediate light vision (mesopic vision) [14]. The ipRGC cells receive stimuli from the rod and cone cells, and also have photopigments (melanopsin). Rod and cone cells are responsible for the initial constriction related to PLR (0.2–1.5s), and ipRGCs cells are responsible for maintaining pupillary constriction, response after stimulation (PIPR), and to regulate circadian rhythm [15].

The specificity of each type of photoreceptor cell means that its responses and behavior are directly associated with the color (wavelength of light), intensity, angle and duration of stimulation [16]. Therefore, devices that perform pupillometry must be configurable and allow the alteration of these parameters.

We performed a careful analysis in an attempt to find reference values that indicated the best configuration or even the best protocol to be used for recording. There are many variables involved in this process and the information presented in the articles was inconclusive. It was not possible to identify two articles that evaluated the same pathology using the same recording protocol and the same techniques, such as computational algorithms or image datasets.

However, there was a possibility that the recording protocol interfered with the efficiency of the method, but it is not possible to make this statement based on the existing studies. Xiaofei Fan et al. [17] and Georgina TF Lynch et al. [18] conducted research to identify autism and

**Table 1**
Pupillometer devices.

| No.[a] | Device | Percent |
|---|---|---|
| 20 | NeurOptics NPi-200 (NeurOptics Inc., Irvine, CA, USA) | 17% |
| 15 | RAPDx (Konan Medical USA, Irvine, CA, USA) | 13% |
| 14 | ViewPoint EyeTrackers (Arrington Research, Scottsdale, AZ, USA) | 12% |
| 10 | Compact Integrated Pupillograph (CIP; AMTech, Dossenheim, Germany) | 8% |
| 8 | MonPack One Software (Metrovision, Perenchies, France) | 7% |
| 7 | NeurOptics NPi-100 (Neuroptics Inc., Irvine, CA, USA) | 6% |
| 7 | EyeLink 1000 eye tracker (SR Research, Ottawa, ON, Canada). | 6% |
| 6 | NeuroLight AlgiScan (iDMed, Marseille, France) | 5% |
| 6 | Neuroptics DP-2000 binocular pupillometer (NeurOptics Inc., Irvine, CA, USA) | 5% |
| 4 | Iriscorder Dual C10641 (Hamamatsu Photonics, Hamamatsu, Japan) | 4% |
| 4 | Neuroptics PLR-2000 (Neuroptics, Irvine, CA, USA) | 4% |
| 4 | TOBII eye tracker (Tobii AB, Danderyd, Sweden) | 4% |
| 3 | ETL-100H Pupillometry Lab (ISCAN Inc., Woburn, MA, USA) | 3% |
| 3 | GC660 (Allied Vision Technologies, Stadtroda, Germany) | 3% |
| 2 | RK-7261(ISCAN, Inc., Woburn, MA, USA) | 2% |

[a] Number (No.) of studies.

obtained accuracies of 92.5% and 72.2% respectively. The recording protocols adopted were different, but the patients examined by [17] were children while [18] examined adolescents, making it impossible to determine how much the difference in recording protocols influenced the accuracy obtained and how much the difference in examined classes interfered in the final result.

It was also possible to identify in other studies that investigated other pathologies that the presented accuracy differed as well as the protocol. However, until further studies assess the impact of these differences, the definition of the protocol should be carried out based on the characteristics of the pathology and class of individual analyzed. The main components of the existing protocols are presented below.

#### 3.2.1. Brightness of the capture environment

Due to the photo sensitive characteristic of the Rod and Cone cells, the brightness of the environment where the images will be captured can significantly alter pupillary measurements. Ong et al. [19] claim that in order to produce valid results and with maximum reliability, examiners should standardize this luminosity.

#### 3.2.2. Wave-length

The wavelength defines the color of the light that will be used in the stimulation, and the most frequent are the blue and red monochrome lights. White light stimulation was preferred by research done prior to 2012 and also when studies were related to brain injuries. Stimulation with monochromatic light, however, has become the trend in more recent research, especially in the assessment of post-lighting response.

Paul Richter et al. [20] claim that blue light causes greater pupillary reflections than other colors. Park et al. [21] say that in order to access the rod response, stimulus in blue light should be used and the most suitable for cone cell reactivity is red light at a low intensity. The authors also conclude that the best way to assess the response of melanopsin cells is with blue monochromatic light applied with high intensity.

#### 3.2.3. Stimulus duration

Light stimulus is usually applied in pulses with durations varying from a few milliseconds to seconds, or in flickers at a certain frequency (Fig. 3). Park et al. [21,22] claim that it is possible to isolate the contributions of rod, cone, and melanopsin cells with 1 s of stimulation. Shaobo Lei et al. [16] state that between 4 and 200 ms, PIRP activity increases with longer duration. However, according to the authors, after 400 ms there is no increase in pupillary reactivity. Therefore, according to them, the necessary stimulus to measure the activity of the PIRP characteristics does not need to exceed 400 ms.

#### 3.2.4. Intensity

The intensity of light applied to the pupil is often measured in lux (lx), lumen (lm) or candela (cd). Lumen is the amount of light measured through a light emitting point. Lux is the incidence of light at one point. By definition one lumen has an illuminating capacity equivalent to one lux in one square meter. Candela is defined by the luminous intensity, which is the uniform distribution that falls from a point to a certain place. Park et al. [21] state that rod activity is best studied with low intensity stimulus, cone and melanopsin cells require high intensity flashes presented after adaptation to the dark. Shaobo Lei et al. [16] state that PIPR increases monotonically with increasing stimulus intensity ranging from 0.1 to 400 $cd/m^2$.

#### 3.2.5. Adaptation period

This concerns the time it takes for the rod and cone cells to adapt to ambient lighting. It refers to the initial adaptation, before pupillary measurement or adaptation between stimulations. Park et al. [21] suggests that 10 min of initial adaptation to the dark be given before performing tests on pupillary reflex. Bin Wang et al. [23] suggest 20 min of adaptation to the dark. Ken Asakawa et al. [14] in turn claim that natural lighting is sufficient to capture the cone response with 5 min of light adaptation. They also suggest that the rod response can be obtained after at least 10 min of adaptation to the dark.

#### 3.2.6. Accommodation between stimuli

Rod and cone cells need time to accommodate to lighting. If accumulated influence is not the subject of study, research that applies more than one period of stimulation should wait for some time to allow accommodation between stimulus. This time is necessary for the pupillary diameter to return to its original state [24–26]. Otherwise, the response produced by subsequent stimulus will be influenced by the previous stimulus.

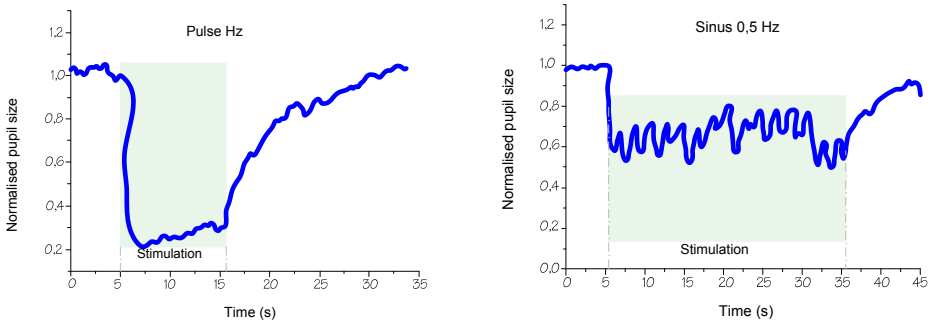
#### 3.2.7. Direct or consensual response

Pupillary reflex to light can be induced directly in the eye to be evaluated, and the reflex used here is the direct one. Conversely, it can be induced by the other eye (since the pupillary contraction occurs in a synchronized way), in which case the reflex used is the consensual one. Sindri Traustason et al. [27] state that normally there is no difference between the direct or consensual response with blue lighting. However, with red lighting, the authors state that there is a slightly greater response during consensual lighting, when compared to direct.

#### 3.2.8. Number of stimulation repeats

Most of the research found stimulated the pupil only once, however, some pathologies could be identified by measuring the time that cells need to return to their original state after stimulation, and their reaction to a second stimulus. The article by Daniel M Bittner et al. [28] repeated the stimulation 40 times, aiming to investigate changes in the reflex of the pupil to the light of people with Alzheimer's disease.

Table 2 summarizes the recording and stimulation protocols found in the research using PLR to aid diagnostics. The 'Aspect' column shows the different ways of performing pupillometry. The column 'Range' shows




(a) 10-s pulse (b) 0.5-Hz

**Fig. 3.** Pupil responses to chromatic light at a single 10-s pulse stimulus (a) and a flicker 0.5-Hz.

**Table 2**
Stimulation and recording protocol.

| Id. | Aspect | Range | Mode[a] |
|---|---|---|---|
| 1 | Luminosity | Scotopic, Mesopic, Photopic | Scotopic |
| 2 | Wavelength | White, Blue, Red, Green, Yellow | White |
| 3 | Reflex | Direct, Consensual, Both | Consensual |
| 4 | Stimulus Duration | 10 ms–2 m | 1 s |
| 5 | Intensity | 1–1000 lux | 100 lux |
| 6 | Repeat Recordings | 1–40 times | 1 time |
| 7 | Initial Accommodation | 2 s–40 min | 10 min |
| 8 | Accommodation between Measurements | 100 ms–15 min | 30 s |

[a] Most frequently used in studies.

the occurrences or the interval of occurrences of each aspect. As instance, luminosity used by authors in their experiments was scotopic, mesopic, or photpic. The 'Mode' column reports the most frequently occurrence for each aspect, for instance, the most frequent kind of luminosity been scotopic.

The analysis of the protocols showed several ways of performing pupillometry. The definition of each aspect of the protocol is associated with the behavior of the photoreceptor cells that will be evaluated.

### 3.3. Pupil detection and segmentation

In order to perform computerized pupillometry, it is essential that pupil detection and segmentation are performed. The segmentation in the images is done by precisely delimiting the edges and extracting the region of interest.

Although it is an important stage of pupillometry, most of the research that sought to aid diagnostics did not mention the method of detection and segmentation used. An explanation for this absence is due to the fact that commercial pupillometers have satisfactorily solved the problem of pupil detection and segmentation in an environment with controlled lighting (e.g. closed room, helmet or glasses that control the entry of light). Another explanation for this is that in many of the articles the objective was in another part of the process, with segmentation being treated as a secondary process and therefore was not presented in detail.

Eighteen articles were found that presented the process of detection and segmentation of the pupil. An overview of the algorithms is presented below. The Table 3 summarizes these algorithms.

Pupillary detection in real-world conditions still presents challenges such as changes in lighting conditions, distance and angle of shooting, reflections, or the use of glasses, masks or contact lenses. Research that sough to develop methods for pupil detection, such as Swirski, SET, ExCuSe, ELSe, PupilNet, Pure, PuResT, tried to improve pupil measurement and increase robustness when performed in an uncontrolled environment.

The StarBust [29] algorithm initially locates and removes reflections from the image. It then locates the edges using an iterative technique based on characteristics. Then an ellipse is fitted to the subset of edge points using the *Random Sample Consensus - RANSAC* [30] paradigm. The best fit parameters are used to initialize a local search model for the ellipse parameters that maximize the fit of the image data.

The SET algorithm in Javadi et al. [31] assumes that the pupil is circular. The image is binarized and related pixels are segmented into groups. Segments that contain less than a certain number of pixels are discarded. For the remaining segments, ellipses are fitted. The ellipse that is most circular is selected as the center of the pupil.

The ExCuSe algorithm proposed by Fuhl et al. [32] is based on edge detection and ellipsis nesting. It uses the Canny [33] edge detector with refined morphological operations. It presents the edges of the ellipses in order to find the best edge. A second algorithm detects the estimated position of the pupil using an integral angular projection function and refines that projection until convergence.

The Swirski et al. [34] estimated pupil contours by first applying *Haar-like features* to find the pupil region, then segmented the pupil region by grouping the histograms with k-means and applying the Canny edge detector. Finally, it used RANSAC to estimate pupillary contour.

The authors of PupilNet [35] and its respective improvement PupilNet V2.0 [36] propose a method of pupil detection in IR images composed of a pipeline of two CNNs. The first identifies the position of the pupil and the sub-regions of interest not so precisely, while the second refines the pupil position using the sub-regions and the estimated initial position.

The ElSe algorithm also proposed by Fuhl et al. [37] also used Canny

**Table 3**
Pupillary detection and segmentation.

| Id. | Name | Year | Ref | Techniques | Data Set | Ilumi | Detection | Accuracy(%)[1] |
|---|---|---|---|---|---|---|---|---|
| 1 | StarBust | 2005 | [29] | RANSAC | LPW | IR | Pupil | 16.65[2] |
| 2 | Swirski | 2012 | [34] | Haar Wavelets, Kmeans, RANSAC | LPW | IR | Pupil | 49.76[2] |
| 3 | SET | 2015 | [31] | Convex Hull, Ellipse Fitting | LPW | IR | Pupil | 29.42[1] |
| 4 | ExCuSe | 2015 | [32] | Histogram, Angular Integral Projection, Ellipse Fitting | LPW | IR | Pupil | 47.79[1] |
| 5 | ELSe | 2015 | [37] | Canny, Ellipse Fitting | LPW | IR | Pupil | 68.92[1] |
| 6 | ESCaF | 2018 | [38] | Canny, Elipse Fitting | LPW | IR | Pupil | 73.23 |
| 7 | PuRe | 2018 | [39] | Canny, Morphological Operations, K-Cosine Chain | ExCuSe, ElSe | IR | Pupil | 76.71[2] |
| 8 | PuReST | 2018 | [43] | Canny, Morpholocial Operations, Mask of Previous Pupil | Swirski, ExCuSe, ElSe, LPW, PupilNet | IR | Pupil | **87.62** |
| 9 | Setiawan et al. | 2018 | [40] | Circular Hough Transform | CASIA | IR | Pupil | 80.00[3] |
| 10 | PupilNet | 2016 | [35] | CNN | ExCuSe | IR | Pupil | 65.88 |
| 11 | PupilNet 2.0 | 2017 | [36] | CNN | Else, Excuse, PupilNet | IR | Pupil | 79.60 |
| 12 | Vera-Olmos | 2017 | [41] | CNN | ExCuSe, ElSe | IR | Pupil | 82,17 |
| 13 | Han | 2019 | [42] | UNet-CNN | ExCuSe, ElSe, | IR | Pupil | 83.00 |
| 14 | RAPDNet | 2019 | [44] | CNN, Circular Hough | ElSe | IR | Pupil | 90.60 |
| 15 | Miron et al. | 2019 | [46] | CNN | ExCuSe | IR | Pupil | **92.91** |
| 16 | Kitazumi | 2018 | [48] | CNN | UBIRIS.v2, GI4E | VL | Eye/ Pupil | **80.10 UBITID. v2** 98.62 GI4E |
| 17 | Choi | 2019 | [50] | CNN | BioID, GI4E | VL | Eye/ Pupil | 93.30 BioID **99.60 GI4E** |
| 18 | Zhao | 2019 | [47] | Ada Boost algorithm, Canny, Circular Hough | BioID, FERET | VL | Eye/ Pupil | **96.40 BioID 97.90 FERET** |

Identifier (Id.), Reference (Ref.), Near Infra Red (IR), Illumination (Illumi.), Visible Light. (VL), Accuracy (Acc.). [1]Capacity to find the center of the pupil in the database images, with a tolerance of up to five pixels. [2]Data obtained from the study [38]. [3] With 70% of Pupil Occlusion. The best accuracy per approach and database is in bold (i.e. using classic image processing techniques, using artificial neural networks).

and morphological operations to detect edges, but selected the best edge using heuristics such as shape and encapsulation. The edges were then used to fit ellipses and return the center of the pupil and its outline.

George and Aurobinda proposed ESCaF [38], a pupil center detection algorithm that uses both edges and intensity information, along with the candidate filtering approach to identify the best pupil. They claimed to get better performance than with the ELSe algorithm.

PuRe [39] uses Canny as a detector to select segments with curved edges of the pupil outline. It has greater accuracy than PupilNet, which is based on Convolutional Neural Networks (CNN). It loses to Vera Olms in accuracy, but according to the authors, it has less processing time.

Setiawan et al. [40] proposes a methodology using the hough circle transform to locate the pupil in images with occlusion. They claim to have better performance when the pupil is between 70 and 90% covered.

Vera-Olmos and Malpica [41] proposed a method based on CNN which, according to the authors, surpassed the accuracy of previous research by 19%.

Han et al. [42] proposed the indirect use of CNN based on CNN U-Net to first segment the pupil region and then find its center of mass.

PuReST [43] is an improvement on PuRe, which increased performance by 5.44%. It uses information from the current and previous frames to improve performance, so it is classified as a *Pupil Tracker*.

Dogancan Temel et al. [44] used the AlexNet [45] algorithm, which was trained with ImageNet to classify generic objects into 1,000 classes. These models were transformed from object recognition into a pupil detector using the convolutional layers of the network that generate visual representations. The adapted algorithm obtained an accuracy of 90.60%.

Also based on IR images obtained from devices mounted on the head, Miron et al. [46] propose a CNN-based architecture without prior training consisting of 12 convolutional layers and two *max pooling* layers with 108450 prediction parameters. They stated that the approach achieved greater accuracy than ExCuSe, ElSe, ESCaF and PupilNet V2.0 in ExCuSe databases.

Zhiqiang Zhao et al. [47] used the bilateral filtering algorithm to remove noise, performing histogram equalization on the image. After detecting the eye with the Ada Boost classifier, they applied the hough circular transform to identify the center of the pupil. With this algorithm 97.90% accuracy was obtained.

For images obtained with visible illumination (*visible light - VL*), Kitazumi and Nakazawa [48] proposed the use of CNN for center detection and pupillary segmentation in images that do not require IR illumination. They claimed to achieve accuracy more often than presented by Gou et al. [49].

Jun Ho Choi et al. [50] proposed an algorithm using CNN models that first located the landmarks on the faces, and after removing artifacts such as glasses, located the pupil. In their experiments they obtained an accuracy of 99.60% in locating the pupil.

### 3.4. Removing artifacts and filling

Pupillary detection is not always possible due to interference, such as blinking, deviation in the look, reflexes, use of makeup, closed eyelids and other situations that make it difficult to measure the pupillary diameter. In the context of pupillometry, these interferences are called artifacts, which result in missing or erroneous values in the measurement of the pupillometric signal. Identifying and removing these erroneous measurements minimizes the interference of these elements in the analyses, especially those based on statistics.

The techniques found in this SRL for removing artifacts are presented in the Table 4. The application of the Median Filter is the most used.

Additionally, the method proposed by Hershman et al. [51] remove erroneous values that precede and succeed missing values produced by blinks. Initially, it detected the missing values in the pupillometric signal, defined candidate points for the start of the blink and for its displacement, smoothed the data using a 10 ms window to increase the difference between the noise and the pupillary signal. Subsequently, they checked the difference between each pair of consecutive samples, starting with the initial sample (n) the start of the blink moving backward (n - 1) and moving the offset (n + 1) to the end of the blink until a monotonic change in the patter is found, i.e., until the difference between the start and the blink offset is greater than or equal to zero. This way, the interference that the blink causes on the pupillary signal is completely removed.

**Table 4**
Removing artifacts.

| Reference | Removal Technique |
|---|---|
| [52] | Manual Removal |
| [53] | Derivative Filter (200 ms window) |
| [13] | Median Filter (300 ms window) |
| [16] | Median Filter, Low Pass Filter |
| [54] | Median Filter (200 ms window) |
| [55,56,17] | Savitzky-Golay |
| [21] | Median Filter (1s and 500 ms window) |
| [57] | Wavelet and Kalman filter |
| [58,59] | Circularity Coefficient |
| [60] | Removes non-physiological changes based on threshold value |
| [61] | NRMSE |

Normalized Root Mean Square Error (NRMSE).

After removing spurious measurement points, most researchers filled in the gaps in the pupillary signal left by the removal of blinks and other artifacts using linear interpolation to recompose them. The techniques found in this review to recompose the pupillary signal are summarized in Table 5.

### 3.5. Forms of pupillary stimulation

During dynamic pupillometry, whether visual or automated, it is necessary to stimulate the pupil so that its diameter does not remain constant at all times of the measurement making it possible to analyze its behavior towards the stimulus. The ways to stimulate the pupil found in this SLR were:

1. With visible light: which can be done with white or monochromatic light, presented for a few seconds or in brief flashes (flashes), with intensity normally varying between 1 to 100 lux. Stimulation with visible light produces the pupillary response to light, also called a pupillary reflex to light. This response comes from the pupil's primary function of regulating the amount of light reaching the retina and consists of pupillary constriction (miosis) in response to brightness and its dilation in response to darkness. The PLR is considered the most expressive pupillary reflex because it produces the greatest variation in the pupillary diameter over time, when compared to other types of stimulus [72].
2. With cognitive tasks: cognitive load is the amount of activity imposed on working memory [73,74]. Cognitive tasks are activities that demand working memory (mental resources) [75,76] from a person and cause pupillary dilation, through the pupil response evoked by the task (task evoked pupillary response - TEPR), [77].

Cognitive stimuli can be presented as:

**Table 5**
Filling in the pupillary signal.

| Reference | Occurrences | Filling Technique |
|---|---|---|
| [62–64] | | |
| [65–67,24] | | |
| [27,68,69] | 10 | Linear Interpolation |
| [70,56] | 2 | Cubic Interpolation |
| [71] | 1 | Nearest Neighbor |

(a) Visual: demanding cognitive effort in visualizing and performing a task, for example: following an object with the eye, reading words with stroop effect (Stroop Color-Word Test - when a word is printed in a color that differs from the color expressed by the semantic meaning) [78,57,79], performing surgery, performing air traffic control task [80–82].
(b) Hearing: demanding cognitive effort to listen and mentally process tasks, for example: calculating numbers [83], understanding language, listening and memorizing numbers (Digit Span Task) [84–86].

3. With physical exercises: regular resistance training in activities that increase parasympathetic performance [87] such as swimming or running.
4. With emotional activities or excitement: stimuli that arouse emotion or excitement in the participants causing pupillary dilation [88], these stimuli are usually:
   (a) Visual: videos or images with emotional aspects are presented to the volunteers [88–90].
   (b) Hearing: emotional sounds are presented to volunteers [91,91].
5. Activities that cause pain or stress: stimuli that cause or allow the sensation of pain or discomfort in the participants, in this category studies were found that used pain after the effect of analgesia [92,93], pain stimulated by heat [94,95], application of acupuncture [96], use of mouthguard [97], application of shocks on the fingertips [98], cold pressure test (cold pressor test) [99].
6. Substances capable of dilating or contracting the pupil:
   (a) Recreational: opioids [100,101], alcohol [102,61], caffeine [103,104].
   (b) Drugs: analgesics [105], tramadol [106], aripiprazole [107].

Different types of stimuli generate different pupil responses. Luminous stimuli promote pupillary contraction and its subsequent redilation after the end of the stimulus and are directly associated with the activity of the parasympathetic nervous system (SNP) and the sympathetic nervous system (SNS), as seen in Fig. 4. Stimuli that increase arousal or mental effort (cognition) promote pupillary dilation and its subsequent contraction when the stimulus stops producing its effects, as seen in Fig. 5.

### 3.6. Pupil characteristics

Pupillary response to light when measured continuously frame by frame in a video, produces a signal that represents pupillary behavior (pupilogram). This signal shows that the light stimulus produces rapid pupillary contraction (miosis) until it reaches its peak of contraction, which is followed by a smooth redilation (escape) for the duration of the stimulus. When the stimulus is turned off, the pupil re-dilates

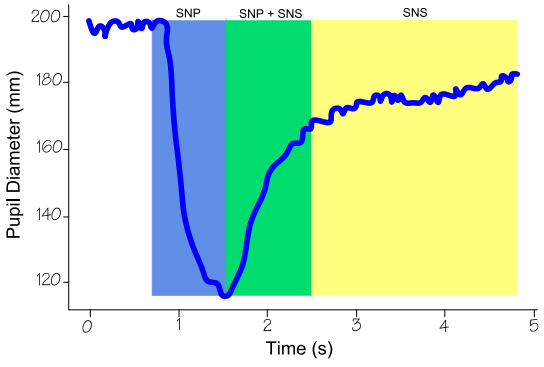



**Fig. 4.** Pupillary reflex to light. Performance of the SNP and SNS - PNS Phase is a fast constriction mainly controlled by PNS; PNS + SNS Phase is a fast redilation under the control of both PNS and SNS; SNS is a slow redilation phase, mainly controlled by SNS activity.

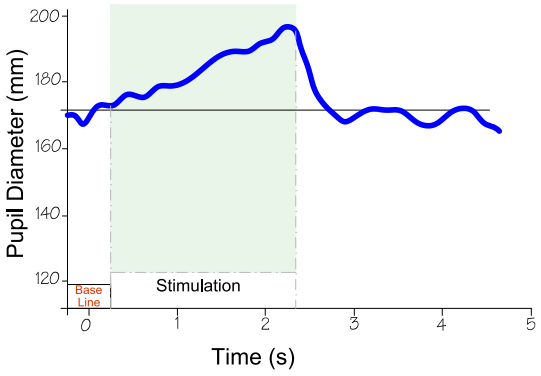



**Fig. 5.** Pupillary reflex to cognitive tasks (e.g. looking at the target and producing manual response).

(mydriasis) and gradually returns to it initial diameter, also called the post-illumination response (post-illumination pupil response - PIPR) [20].

The pupillary signal is generally not fully processed. Researchers sectioned and extracted metrics, i.e., regions that will be measured and evaluated, as in Fig. 6. These metrics are called characteristics (*features*) or descriptors of pupillary behavior. Researches that carried out statistical analysis or applied classical machine learning algorithms to aid diagnoses often compared the values of the characteristics of the control group with those of the group with altered pathology or physiological conditions.

Table 6 presents a summary of the characteristics most present in the studies. Each researched article used a different acronym or nomenclature to name the characteristics studied/ evaluated. In several cases, the same characteristic received different acronyms and names. To facilitate comparison and understanding, Table 6 shows, in addition to the concept, the names and acronyms used for each characteristic and highlights the most used acronyms in bold type.

Characteristics were grouped according to the measurement method used, either static or dynamic. They were also sub grouped by region of pupillary signal, short-term characteristics (transient) of the contraction phase and longer duration characteristics (sustained) measured in the dilation phase.

In addition to the characteristics presented, there were others that were sometimes considered in the studies: (1) Spontaneous fluctuations in pupil size, also called Hippus [108] or pupillary unrest [109] or Spontaneous Pupillary Fluctuation [110] or Pupil Oscillation Frequency (POF) [67] - which are spontaneous variations in pupillary size when it is not being stimulated. (2) Anisocoria of contraction - which occurs when the stimulated pupil (direct reflex) contracts more than the pupil that is not being illuminated (consensual reflex). Anisocyria is calculated

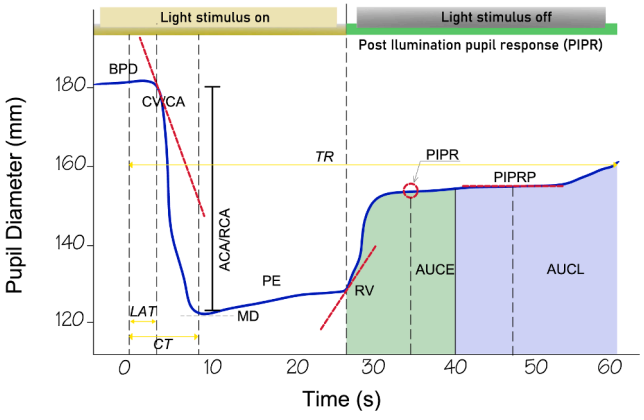



**Fig. 6.** Features of pupillary light reflex.

**Table 6**
Characteristics of the pupillary reflex to light.

| | Name | Initials | Unit | Description |
|---|---|---|---|---|
| **Static** | | | | |
| 1 | Baseline Pupil Diameter or Max Pupil Diameter or Resting pupil Diameter or Initial Diameter | **BPD** MPD RPD D0 | mm | Initial pupil size, determined by the lighting and particular characteristics of each person (ex: race, age, sex). |
| **Dynamic** | | | | |
| [a]Transient | | | | |
| 2 | Constriction Latency or Latency Time Constriction or Time Latency | **LAT** LTC tL | ms | Time required for the effective start of constriction after the start of stimulation. |
| 3 | Minimum Diameter or Peak Pupil Constriction or Max Contraction | **MD** Dmin MC | mm | Smallest diameter achieved during light stimulus application. |
| 4 | Constriction Time or Time to Constriction or Time to Max Constriction | **CT** tC TMC | ms | Time required for the pupil to reach the peak of constriction. |
| 5 | Constriction Velocity or Max Constriction Velocity or Avarage Constriction Velocity | **CV** MCV ACV | mm/s | Constriction movement speed, starting from the initial diameter until reaching the minimum value in a given period of time. |
| 6 | Constriction Acceleration | **CA** | $mm/s^2$ | Variation of constriction speed. |
| 7 | Absolut Constriction Amplitude or Maximum Constriction Amplitude | **ACA** MCA | mm | Difference between the initial diameter and the smallest diameter. |
| 8 | Relative Constriction Amplitude or Percentage of Constriction or Constriction Rate | **RCA** PC CR | % baseline | Difference between the initial diameter and the smallest diameter normalized by the initial diameter. |
| 9 | Pupil Escapes | **PE** | - | Redilation (escapes) that occur during stimulation. |
| [b]Sustained - PIPR [68] | | | | |
| 10 | Redilation Velocity or Dilation Velocity or Max Redilation Velocity [113] or Dilation Speed | **RV** DV MRV DS | mm/s, pixels/s | Redilation speed after the end of light stimulation. |
| 11 | PIPR Amplitude | **PIPR** | % baseline | Pupil size from 3 to 40 s after end of stimulus. |
| 12 | PIPR Amplitude Plateau | **PIPRP** | % baseline | Pupil size in its period stabilization (plateau). |
| 13 | Time to Redilation or PIRP Duration | **TR** | ms | Time required for the pupil to return to a certain percentage of the baseline (50% to 90%). |
| 14 | AUC Early [114] | **AUCE** | - | Area under the curve of the pupillometric signal in the first ten seconds after the end of the stimulus. Calculated as $\sum(BPD - PupilSize)$ 0–10 s. |
| 15 | AUC Late [114] | **AUCL** | - | Area on the pupilometric signal curve from 10 to 30 seconds after the end of the stimulus. Calculated as $\sum(BPD - PupilSize)$ 0–30 s. |
| 16 | Phase Amplitude Percentage [115] or Net PIPR Metrics | **PAP** | unit of metric | Difference of certain metric when stimulation is done with blue light to when done with red light. |

Maximum (Max). [a]Contraction phase. [b]Dilation phase. The most used acronyms are in bold type.

by subtracting the relative constriction amplitude of one eye from the other [111].

Saccadic movements [112] are rapid and simultaneous movements of both eyes between the fixation phases in a certain direction. Although they are not directly related to the pupil, their speed was used in some studies in conjunction with pupil characteristics.

Some researchers used the pupillary characteristics values obtained in each individualized measurement, others chose to use the average of several measurements from the same person.

Not all studies that used PLR to aid the diagnosis described in detail the characteristics used. However, it was clear during the reading of the studies that the characteristics chosen in the investigations determined better or worse accuracy in the results. This happened because each pathology interfered with different regions of the ocular system and therefore with the values measured/represented by the characteristics.

In the last 10 years, studies used PLR for 54 different purposes, largely to assist in the identification of pathologies. Table 7 presents the list of all these applications of PLR and the main characteristics used in the process. Applications that did not describe the characteristics used were omitted.

In some cases, the characteristics were evaluated in an isolated and independent way, and often two or more characteristics or even the variation of a characteristic provides new values investigated by the researchers. Thus, the list of characteristics represents the base variables used to compose each methodology.

Reading the papers showed that 16 different characteristics were investigated. However, it is possible to observe that three characteristics stand out because they were used in more than 50% of the studies, namely: Baseline Pupil Diameter (BPD) used in 37 papers (68. 52%), Constriction Latency (LAT) used in 34 papers (62.96%), and Constriction Velocity (CV) in 29 papers (53.70%).

### 3.7. Applicability of the pupillary reflex to light in auxiliary diagnostics

Studies were found that sought to help obtain different types of diagnoses through PLR. Research on this approach represented about 50% (174/345) of the selected papers and encompassed 54 different types of investigation related to the pupillary reflex to light. Table 8 shows the applications of PLR ordered by the percentage of studies found. Among the studies, the most frequent use of PLR was for Glaucoma with 17 studies (9.77%), followed by Brain Injury with 15 (8.62%) studies, and Diabetes with 14 (8.05%).

In addition to the research mentioned in Table 8 there were also

**Table 7**
Characteristics and pathology applied.

| Purpose | ACA | BPD | CA | CT | CV | LAT | MD | PIPR | PIPRP | RCA | RV | TR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alcohol Abstinence | | | | | CV | LAT | | | | | | |
| Genetic Alteration | | BPD | | | CV | LAT | | PIPR | | RCA | RV | |
| Height | | BPD | | | CV | LAT | | | | | | |
| Alzheimer | | BPD | CA | | CV | LAT | MD | | PIPRP | | RV | TR |
| Amblyopia | | | | | CV | LAT | MD | | | RCA | RV | |
| Obstructive Sleep Apnea | | BPD | | | CV | LAT | | | | | RV | |
| Asthma | | BPD | | | | | MD | | | RCA | RV | TR |
| Autism | | BPD | | CT | CV | LAT | MD | | | RCA | RV | |
| Chagas | ACA | BPD | | | | | | | | RCA | | |
| Chloridemia | ACA | | | | | LAT | | | | | | |
| Convulsions | | BPD | | | | | MD | | | RCA | | |
| Macular Degeneration | ACA | BPD | | | CV | LAT | | PIPR | PIPRP | | | TR |
| Delirium | | BPD | | | CV | LAT | MD | | | RCA | | TR |
| Depression | ACA | BPD | | | | | MD | PIPR | | | | |
| Diabetes | ACA | BPD | | | CV | LAT | MD | PIPR | PIPRP | | RV | TR |
| Pain or Discomfort | | | | | CV | | | | PIPRP | | | |
| DPAR | | BPD | CT | | | LAT | MD | | | | | |
| Drugs (use) | ACA | BPD | | | | LAT | MD | | | RCA | | TR |
| Migraine | ACA | BPD | | | CV | LAT | | | | | | TR |
| Epilepsy | ACA | BPD | | | CV | LAT | | | | | RV | |
| Multiple Sclerosis | | | | | | | | | | RCA | | |
| Nutritional Status | | BPD | | | | | MD | | | | | |
| Medications | | BPD | | | | LAT | MD | | PIPRP | RCA | | |
| Heart Rate | | BPD | CT | | CV | LAT | | | | RCA | | TR |
| Autonomic Ganglionopathy | | BPD | | | CV | LAT | | | | | | |
| Gender | | BPD | CT | | CV | LAT | | | | | | TR |
| Glaucoma | ACA | BPD | CT | | CV | LAT | MD | PIPR | | RCA | | TR |
| Hemianopsia | | BPD | | | | LAT | | | | RCA | | |
| Idiopathic Intracranial Hypertension | | | | | | | MD | PIPR | | | RV | |
| Urinary Incontinence | ACA | BPD | | | CV | LAT | MD | PIPR | | | RV | |
| Cardiac Insufficiency | | BPD | | | CV | LAT | MD | | PIPRP | | RV | |
| Leber | ACA | BPD | | | CV | | MD | | | RCA | | |
| Brain Injury | | BPD | | | CV | LAT | MD | PIPR | PIPRP | RCA | RV | TR |
| Myasthenia Grave | | | CA | | CV | LAT | | | | | | |
| Optic Neuritis | | BPD | | CT | | LAT | | PIPR | | RCA | | |
| Cerebral Palsy | | | | | CV | LAT | | | | | | |
| Parkinson | | BPD | | CT | CV | LAT | MD | PIPR | | RCA | | TR |
| Blood Pressure | | BPD | | CT | CV | LAT | | | | | | |
| Post AC Prognosis | | BPD | | CT | CV | LAT | MD | | | | | |
| Retinitis Pigmentosa | | BPD | | | CV | | | PIPR | | RCA | | |
| Retinopathy | | BPD | | | | | MD | | | | | |
| Unilateral Pseudoexfoliation Syndrome | | BPD | | | CV | LAT | | | | | | |
| Horner Syndrome | | BPD | | | CV | LAT | MD | | | RCA | RV | |
| Sleep or Fatigue | | | | | CV | LAT | | PIPR | PIPRP | RCA | | |
| Smoking | | BPD | | | | | MD | | | | | |
| Essential Tremor | | BPD | CA | CT | | LAT | MD | | | RCA | | |
| TOTAL | 13 | **37** | 3 | 10 | **31** | **34** | 24 | 12 | 8 | 21 | 13 | 12 |

Baseline Pupil Diameter (BPD), Constriction Velocity (CV) and Constriction Latency (LAT) are the most used features in the studies.

those that sought to measure cognitive load (work load), state of stress, emotional state, excitation and state of attention through pupillary response. Although they used computerized pupillometry, they often adopted a different form of stimulation and did not meet the inclusion criteria (I).

Table 9 shows the results of some studies that aimed to classify pathologies and assist in diagnoses. It was observed that the results range from excellent accuracy to others whose results still needs improving. Can be cited as an example of excellent result the work of Shaun M Frost et al. [212] who sought to diagnose Amblyopia and claims to have attained 100% accuracy. By the other hand, can be cited as an example of fail result the study of Wioletta Nowak et al. [191] which sought to diagnose Alzheimer's disease, but presented an error of 46.4% in the prediction of patients and an error of 12.4% in healthy people. This result, however, was improved in subsequent research [190].

The tabulated accuracy values should be considered as indicative of results; however, since the studies did not use standardized methodology and databases, they do not represent a formal comparison between the works.

### 3.8. Classification through the pupillary light reflex

In this section, we will discuss research that used PLR to distinguish between people with pathologies or altered physiological conditions and healthy people with normal physiological condition (no drug use, stress, discomfort, sleep deprivation and others). This distinction or separation is called classification. To make the classification, the researchers used statistical analysis or artificial intelligence techniques.

Those that perform statistical analyses, compared PLR characteristics between groups of people. One of the groups was the control group and the other was comprised of people with some pathology or altered physiological condition. This last group some times was subdivided according to the severity (severity) of the pathology or physiological condition. This type of analysis seeks to identify significant differences in the behavior of pupillary characteristics between groups.

Research using AI techniques most often employed supervised machine learning (when the training phase data is labeled) to find patterns and automatically classify new entries.

The vast majority of research (over 80%) analyzed the statistical significance of the pupillary characteristics between the groups studied.

**Table 8**
Research purposes using PLR to assist diagnostics.

| Id. | Reference | Purpose | Freq. | Device More Used | Best Acc. |
|---|---|---|---|---|---|
| 1 | [12,116–119] [120–122,115] [123,25,124,125] [126,127,53,128] | Glaucoma | 9.77% | RAPDx | 0.87 [12] |
| 2 | [129–133] [134–136,132,137] [138–142] | Brain Injury | 8.62% | NeurOptics NPi-200 | 0.81 [140] |
| 3 | [143–145,113,146] [147–150,26] [151,152,52,153] | Diabetes | 8.05% | ViewPoint EyeTrackers | 0.86 [149] |
| 4 | [154–157] [158–161] [44,162,163] | DPAR | 6.32% | RAPDx | 0.98 [157] |
| 5 | [164,165,112,166,167] [168–172] | Sleep or Fatigue | 5.75% | ViewPoint EyeTrackers | - |
| 6 | [173–176] [177–179] | Post AC Prognosis | 4.02% | NeurOptics NPi-200 | 0.82 and 0.84 [175] |
| 7 | [180,18,17,181] [182,183] | Autism | 3.45% | GC660 | 0.92 [17] |
| 8 | [184,67,185–187] | Optic Neuritis | 2.87% | EyeLink II eye-tracker | 0.77 [67] |
| 9 | [188,189,28,190,191] | Alzheimer's | 2.87% | NeurOptics VIP-200 | 0.89 [189] |
| 10 | [192,65,71,193,194] | Depression | 2.87% | NeurOptics PLR-2000 | - |
| 11 | [20,195–198] | Retinitis Pigmentosa | 2.87% | Customized | 0.97 [198] |
| 12 | [199–202] | Genetic Alteration | 2.30% | CIP (AMTech, Germany) | - |
| 13 | [203–206] | Heart Rate | 2.30% | MonPack One Software | - |
| 14 | [109,207–209] | Parkinson | 2.30% | NeuroLight AlgiScan | - |
| 15 | [210,106,107] | Medication | 1.72% | NeurOptics PRL-200 | - |
| 16 | [93,97,211] | Pain or Discomfort | 1.72% | NeuroLight AlgiScan | - |
| 17 | [212–214] | Amblyopia | 1.72% | NeurOptics VIP-200 | 1.00 [212] |
| 18 | [99,215,216] | Migraine | 1.72% | CIP (AMTech, Germany) | - |
| 19 | [217,218] | Multiple Sclerosis | 1.15% | (NeurOptics, USA) | 0.99 [217] |
| 20 | [219,220] | Blood Pressure | 1.15% | NeuroLight AlgiScan | 0.65 [219] |
| 21 | [221,54] | Obstructive Sleep Apnea | 1.15% | ViewPoint EyeTracker | - |
| 22 | [222,64] | AMD | 1,15% | Customized | 0.90 [64] |
| 23 | [223,100] | Drugs (use) | 1.15% | NeurOptics PRL-200 | - |
| 24 | [224,225] | Epilepsy | 1.15% | RK-7261 | - |
| 25 | [226,227] | Urinary Incontinence | 1.15% | PLR-2000 | - |
| 26 | [228,229] | Leber | 1.15% | Procyon P2000 | - |
| 27 | [230,231] | Liveness | 1.15% | DMK 4002-IR | 1.00 [230] |
| 28 | [232] | Cardiac insufficiency | 1.15% | EyeLink 1000 eye tracker | - |
| 29 | [233,234] | PXS | 1.15% | MonPack One | 0.56 [233] |
| 30 | [102,61] | Alcohol (use) | 1.15% | Customized | 0.90 |
| 31 | [235] | Alcohol Abstinence | 0.57% | CIP (AMTech, Germany) | - |
| 32 | [236] | Height | 0.57% | CIP (AMTech, Germany) | - |
| 33 | [111] | Anisocoria | 0.57% | Customized | - |
| 34 | [237] | Asthma | 0.57% | NeurOptics NPi-200 | - |
| 35 | [238] | Chagas | 0.57% | - | - |
| 36 | [63] | Chloridemia | 0.57% | NeurOptics DP-2000 | - |
| 37 | [239] | Convulsions | 0.57% | NeurOptics NPi-100 | - |
| 38 | [240] | Delirium | 0.57% | NeurOptics NPi-200 | 0.93 |
| 39 | [241] | Neurological Development | 0.57% | GC660 | - |
| 40 | [242] | Virtual Reality Sickness | 0.57% | - | - |
| 41 | [243] | AAG | 0.53% | (NeurOptics. USA) | - |
| 42 | [244] | Gender | 0.53% | - | - |
| 43 | [245] | Hemianopsia | 0.53% | CIP (AMTech. Germany) | - |
| 44 | [13] | IIH | 0.53% | ViewPoint EyeTrack | 0.85 |
| 45 | [246] | Mercury Poisoning | 0.53% | Roland Consult Pupillometer | - |
| 46 | [247] | Myasthenia Severe | 0.53% | Customized | - |
| 47 | [248] | Nutritional Status | 0.53% | - | - |
| 48 | [249] | Cerebral Palsy | 0.53% | Penlight | - |
| 49 | [250] | Retinopathy | 0.53% | - | - |
| 50 | [251] | Allergic Rhinitis | 0.53% | OPD-Scan III (NIDEK Co. Japan) | - |
| 51 | [11] | Horner Syndrome | 0.53% | NeurOptics NPi-200 | 0.8460 |
| 52 | [252] | Intraocular Suppression | 0.53% | NeurOptics NPi-200 | - |
| 53 | [253] | Smoking | 0.53% | Corneal Topography-Aberrometer (OPD Scan. Japan) | - |
| 54 | [24] | Essential Tremor | 0.53% | iView X Eye-tracker 1250 | - |

Identifier (Id), Frequency (Freq), Age-related Macular Degeneration (AMD), Pseudoexfoliation Syndrome (PXS), Compact Integrated Pupillograph (CIP), Autoimmune Autonomic Ganglionopathy (AAG), Idiopathic Intracranial Hypertension (IIH).

**Table 9**
Accuracy of research using PLR to diagnose pathological or physiological conditions.

| | Reference | Purpose | Classificator | Precision[1] |
|---|---|---|---|---|
| Excellent | [212] | Amblyopia | ROC analysis | AUC = 1.000 |
| | [217] | Multiple Sclerosis | Statistic Test | AUC = 0.990 |
| | [157] | DPAR | Statistic Test | AUC = 0.980 |
| | [198] | Retinitis Pigmentosa | Statistic Test | AUC = 0.970 |
| Good | [61] | Alcohol (use) | SVM | ACC = 0.900 |
| | [64] | Macular Degeneration Age Related | Statistic Test | AUC = 0.900 |
| | [178] | Post HA Prognosis | Statistic Test | AUC = 0.880 |
| | [149] | Diabetes | Statistic Test | AUC = 0.860 |
| Fair | [67] | Optic Neuritis | Statistic Test | AUC = 0.820 |
| | [115] | Glaucoma | Statistic Test | AUC = 0.740 |
| | [18] | Autism | LDA | AUC = 0.720 |
| Poor | [145] | Diabetes | Statistic Test | AUC = 0.690 |
| | [219] | Blood Pressure | Statistic Test | AUC = 0.650 |
| | [214] | Amblyopia | Statistic Test | S: 0.650 E: 0.650 |
| Fail | [233] | Pseudoexfoliation Syndrome Unilateral (PES) | Statistic Test | AUC = 0.560 |
| | [191] | Alzheimer | Random Forest | ACC = 0.536 |

[1]Excellent = [1.00–0.91], Good = [0.90–0.81], Fair = [0.80–0.71], Poor= [0.70–0.61], Fail = [0.60–0.00]. Heart Attack (HA), Support Vector Machine (SVM), Area Under the Receiver Operating Characteristic Curve (AUC), Accuracy (ACC), Linear Discriminant Analysis (LDA), Sensitivity (S), Specificity (E).

However, with the evolution of Artificial Intelligence techniques, more and more works have used these tools.

Table 10 lists the AI techniques that were used by studies to classification and assist diagnoses based on light stimulation. As may be seen, the SVM (Support Vector Machine) was the most used. Convolutional neural networks were preferred to perform detection and segmentation of the pupil.

## 4. Discussion

When analyzing the data collected, it was found that the pupilometer most used in the research was the NeurOptics NPi-200 (NeurOptics Inc., Irvine, CA, USA) (answering Q1). This device was used mainly in research that investigated brain injuries and autonomic dysfunction. However, several studies, either due to cost or to the peculiarities of the study itself, did not use commercial pupillometers, preferring to develop their own devices.

Table 2 shows the most used stimulation protocols (answering Q2). It is noteworthy that the most frequent protocol sometimes coincided with the one suggested in the research that sought to define a practical and adequate protocol for pupillometry. For example, an initial adaptation period of 10 min and the duration of the stimulus of 1 s are the most used in the research, and were in accordance with the recommendation of Asakawa et al. [14].

Scotopic luminosity was the most common among the studies, and presented benefits such as reduction of the reflections on the image, standardization of the luminosity, and potentiation of the contraction amplitude, since in a dark environment, the pupil will be at its maximum dilation. White light stimulation was the most frequent, and was effective when the objective of the research was related to brain injury and autonomic dysfunction, usually performed at an intensity of up to 100 lux. Research aimed at defining the protocol [21,20], suggested that blue was the most effective for analyzing rod functions and red was the most effective for analyzing cone functions.

The use of consensual reflexes was the most usual, as it allowed filming to produce images with fewer reflexes. The recorded pupil did not receive the light stimulus directly and, therefore, there was no need to treat the light reflexes that would be generated by the stimulation.

Regarding the detection and pupillary segmentation methods, Table 3 shows the main computational methods used to locate and measure pupil diameter (answer to Q3). In this overview, the PuReST algorithm stood out, and presented the best performance for a purely algorithmic algorithm. The algorithm proposed by Miron et al. that used an approach based on Convolutional Neural Networks was noteworthy.

In order to detect blinking, most surveys applied a median filter with a window ranging from 200 ms to 1s, which is technique the most used to treat blinks and artifacts (answer to Q4). It is based on the fact that pupillary reactions occur gradually over time, so changes in pupil diameter that are too abrupt are considered noise.

Table 8 shows which diagnoses pupillometry has helped, the percentage of this type of study in relation to the total of studies found, the device most used by type of diagnosis, and the best accuracy in detecting the pathology or physiological condition.

The diversity of possible diagnoses through pupillary reflex to light is to be highlighted. It may also be seen that studies on glaucoma were the most frequent, followed by studies on diabetes, brain injuries, relative afferent pupillary defects, and tiredness or fatigue.

Complementing the investigation of PLR applications (answer to Q5), Table 7 shows the characteristics most used in each study and maximum pupil diameter at rest, the latency calculated at the beginning of the contraction, and the speed of the contraction were present in more than half of the studies.

Table 10 allows us to see different levels of accuracy in the research on the PLR in diagnoses, ranging from excellent to not so promising (answer to Q6) thus confirming that this safe and non-invasive technique can be very useful in helping the diagnosis of several pathologies.

Regarding the artificial intelligence techniques that are usually used (answer to Q7), it is clear that there is much to be explored in this area. Most research aimed at diagnosis was restricted to statistical analysis of pupil behavior (94%), and only a fraction used AI techniques (6%). When there is sufficient data for training, AI techniques have been shown to be efficient and can be used to aid diagnosis. Deep Neural Networks have been used in pupillary detection; however, research that used them directly in the classification of pathologies or in aiding diagnosis were not found in this SLR.

**Table 10**
Research using AI tools for classification.

| Reference | Purpose | Year | Techniques | Accuracy |
|---|---|---|---|---|
| [17] | Autism | 2009 | Perceptron algorithm | 0.9250 |
| [230] | Liveness | 2015 | SVM | 1.0000 |
| [254] | Biometry | 2015 | SVM | 0.8873 |
| [191] | Alzheimer | 2016 | Rando Florest | 0,8760 healthy, 0.5360 diseased |
| [255] | Age/ Overweight | 2017 | K-means | C1: 0.3330 C2: 0.8750, C3: 0.2500, C4: 0.7770 |
| [150] | Diabetes | 2017 | SVR | 0.3730 |
| [102] | Alcohol (use) | 2015 | SVM | 0.8519 |
| [61] | Alcohol (use) | 2018 | SVM | 0.9048 |

## 5. Recommendations for the use of Pupillometry

Due to pupillary physiology and its way of reacting to light stimulation, research that used PLR to assist in diagnoses adopted certain procedures to minimize interferences that may bias the analyses, some of which are listed below:

1. The group of people to be used as a control must not have ophthalmic diseases [88], use drugs or caffeine and, for Duque et al. [54], should avoid eating chocolate and bananas. They must also be in normal conditions regarding hours of sleep, rest, stress and emotional state.

2. A focal point should be used so that the participants fix their gaze during the performance of the pupillometric tests. This measure aims to minimize interference of the accommodative pupillary response responsible for adapting to the distance and size of the visualized object [256]. This accommodation is also known as pupil near response [15], responsible for constricting the pupil when looking at a nearby object and for dilation when looking at a distant object.
3. The time for filming should be standardized. It is recommended that it be done at the same time of day to minimize the influence of the variation of the circadian cycle of each participant [88].
4. Before pupillometry is performed, wait until the pupil adapts to the ambient light. This period must be at least 10 min, as mentioned in Section 3.2.5.
5. To minimize interpersonal variation in pupil size, caused by factors such as genetics, ethnicity, age, and sex, pupil characteristics should be normalized for the period prior to the application of the stimulus (*baseline*) [257,151].
6. It is also necessary to pre-process the data as suggested by Kret and Sjak-Shie [258] in four steps: (1) Prepare raw data for processing (remove negative values, normalize data, delete videos with excess artifacts); (2) Filter the data to remove extreme values with pupil diameters larger or smaller than physiologically possible (1.5 to 9 mm), remove *outliers* and isolated values, remove outliers in terms of speed of expansion or contraction (ie, with size variation disproportionate to neighboring diameters); (3) Processing valid values, for example, calculating the average between the behavior of both eyes or interpolating missing values; (4) Analyze the characteristics individually to determine if they are consistent. For this, it is possible to calculate average, minimum values, maximum values, standard deviation and percentage of missing data.
7. Keep the environment where the tests will take place pleasant enough not to disturb the participants. This measure seeks to prevent the pupil, in addition to reacting to the amount of light reaching the retina, from also reacting to excitement, emotions, pain, stress or discomfort [259].

## 6. Limitations of this study

1. The initial search filter was limited to the Title and Summary of articles, which may theoretically have leaft out from the SRL studies that did not mentioned in these sessions the intention of using PLR for diagnostics.
2. Although there are several ways to stimulate the pupil, as can be seen in Section 3.5, the emphasis of this SRL was on research that used light as a form of stimulation.
3. The quality of the studies included in this review has not been formally assessed. This can generate bias in the quantitative analyzes, since, no additional weight was given to research published in renowned journals or congresses.
4. In the purpose section, the study sometimes referred to more than one purpose, usually DPAR and Glaucoma. In these cases, the research purpose defined for the article was the one that received the most emphasis.

## 7. Conclusions

PLR is a practical, non-invasive, low cost technique whose efficacy has been proven by several studies. Although multiple factors can influence the pupillary diameter, in standardized conditions and with the necessary care, it can help diagnoses ranging from analysis of the neurological condition to possible pathologies or altered physiological states.

The application of pupillometry requires that certain care be taken. The pupil's physiology must be cared for and be given time to adapt to ambient light. Stimulation should be done with the appropriate color, duration and intensity. Reflexes other than the luminous must be prevented from interfering in the analysis of the pupillometric signal. The accommodative reflex can be avoided by placing a focal point on the pupilometer so that the participant fixes the gaze on it. The tests should be conducted in calm and pleasant environments to avoid the influence of stress or excitation on the pupillary reflex. The group of people used as a control must not suffer from pathologies related to pupillary behavior or be in an altered physiological condition.

As for the computational techniques employed, a device with a configurable recording protocol must be used. The algorithm for detection and segmentation must have good accuracy. PuReST proved to be an efficient algorithmic approach and the CNN-based algorithm proposed by Miron et al. proved to be efficient using AI. To improve the quality of the data obtained in the tests, blinks and noise that occur during the recordings must be removed. The algorithm proposed by Hershman et al. may be an option. The data must also be processed and the characteristics of the signal extracted.

Lastly, in the classification phase, it was noted that most research only performed statistical analyses of pupillometric characteristics. The constant evolution of artificial intelligence techniques, and the growing number of pupillometric tests available, make room for AI tools to complement the statistical analysis of the data and produce information to assist doctors and specialists in diagnosing pathologies and physiological conditions.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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