Exploring Pupillometry as a Tool for Early Detection of Genetic Diseases in Children

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Abstract:

Inherited retinal diseases cause severe visual deficits in children. They are classified in outer and inner retina diseases, and often cause blindness in childhood. The diagnosis for this type of illness is challenging, given the wide range of clinical and genetic causes (with over 200 causative genes). It is routinely based on a complex pattern of clinical tests, including invasive ones, not always appropriate for infants or young children. A different approach is thus needed, that exploits Chromatic Pupillometry, a technique increasingly used to assess outer and inner retina functions. This paper presents a novel Clinical Decision Support System (CDSS), based on Machine Learning using Chromatic Pupillometry in order to support diagnosis of Inherited retinal diseases in pediatric subjects. An approach that combines hardware and software is proposed: a dedicated medical equipment (pupillometer) is used with a purposely designed custom machine learning decision support system. Two distinct Support Vector Machines (SVMs), one for each eye, classify the features extracted from the pupillometric data. The designed CDSS has been used for diagnosis of Retinitis Pigmentosa in pediatric subjects. The results, obtained by combining the two SVMs in an ensemble model, show satisfactory performance of the system, that achieved 0.846 accuracy, 0.937 sensitivity and 0.786 specificity. This is the first study that applies machine learning to pupillometric data in order to diagnose a genetic disease in pediatric age.

Keywords: Machine Learning, Retinal Diseases, Eye, Retina, Pediatric, Chromatic Pupillometry, Pupillometeric Data, Diagnose, Retinitis Pigmentosa

1. INTRODUCTION

Inherited Retinal Diseases (IRDs) represent a significant cause of severe visual deficits in children. They frequently are cause of blindness in childhood in Established Market Economies (1/3000 individuals). IRDs can be divided into diseases of the outer retina, namely photoreceptor degenerations (e.g., Leber Congenital Amaurosis, Retinitis Pigmentosa, Stargardt disease, Cone Dystrophy, Achromatopsia, Choroideremia, etc.), and diseases of the inner retina, mainly retinal ganglion cell degeneration (e.g. congenital glaucoma, dominant optic atrophy, Leber hereditary optic neuropathy). Both conditions are characterized by extremely high genetic heterogeneity with over 200 causative genes identified to date, which represent a remarkable obstacle to a rapid and effective diagnosis.

A. CURRENT CLINICAL EVALUATION METHODS

The clinical evaluation of IRDs is routinely based on a complex pattern of clinical tests, including invasive ones, that are not always appropriate for infants or young children. For example, electrophysiological testing, that represents the most informative clinical investigation for the diagnosis of inner and outer retinal diseases, often requires sedation of the children. Sedation affects the retinal response and requires a complex healthcare environment with high costs for the health system. Therefore, the clinical diagnosis is not easy and requires specialized centres. Consequently, it takes a long time for the young patients and their relatives to receive a correct and complete screening. In many cases the electrophysiological responses are below the noise level (for example, extinguished scotopic electroretinogram response is the condition confirming the diagnosis). These responses are therefore not suitable for monitoring changes in visual functionality, that is relevant for evaluating disease progression and therapy efficacy.

B. PUPILLOMETRY

A novel approach to support the diagnosis of IRDs would be useful. To this regard, chromatic pupillometry has been proposed as a highly sensitive and objective test to quantify the function of different light-sensitive retinal cells and, therefore, it has been shown helpful to detect the retinal dysfunction caused by IRDs as summarized. Photoreceptor cells (rods and cones) exhibit fast temporal kinetics and cause a brisk pupillary constriction in response to light, whereas the inner retinal melanopsin containing intrinsic photosensitive Retinal Ganglion Cells (ipRGCs) exhibits slower temporal kinetics and elicits a sustained pupillary constriction to light stimuli, persisting after light cessation. The relative contributions of the three receptor types (rod, cone, and melanopsin photopigments) to the Pupillary Light Reflex (PLR) have been examined by manipulating the characteristics of large-field (90) flash stimuli and the adaptation conditions (light vs. dark adapted). For example, high-luminance, long-wavelength (red) flashes presented against a rod-suppressing adapting field elicit a PLR that is predominately cone-mediated whereas low-luminance,

short-wavelength (blue) flashes presented to the dark-adapted eye elicits a PLR that is primarily rod mediated. For high-luminance, short-wavelength flashes presented to the dark-adapted eye, there is an initial transient pupil constriction (rod- and cone-mediated) that is followed by a melanopsin-mediated sustained constriction that can last for more than 30s after stimulus offset. The prolonged melanopsin-mediated constriction has been used in clinical protocols to assess inner-retina function. Thus, the use of chromatic pupil responses may be a novel way to diagnose and monitor diseases affecting either the outer or inner retina. This evidence suggested that a clinical decision support system (CDSS) based on chromatic pupillometry could be developed to support diagnosis of IRDs.

2. LITERATURE SURVEY

Genotype–phenotype correlation and mutation spectrum in a large cohort of patients with inherited retinal dystrophy revealed by next-generation sequencing.

AUTHOR: X.-F. Huang, F. Huang, K.-C. Wu, J. Wu, J. Chen, C.-P. Pang, F. Lu, J. Qu, and Z.-B. Jin,

Purpose: Inherited retinal dystrophy (IRD) is a leading cause of blindness worldwide. Because of extreme genetic heterogeneity, the etiology and genotypic spectrum of IRD have not been clearly defined, and there is limited information on genotype-phenotype correlations. The purpose of this study was to elucidate the mutational spectrum and genotype-phenotype correlations of IRD. Methods: We developed a targeted panel of 164 known retinal disease genes, 88 candidate genes, and 32 retina-abundant microRNAs, used for exome sequencing. A total of 179 Chinese families with IRD were recruited. Results: In 99 unrelated patients, a total of 124 mutations in known retinal disease genes were identified, including 79 novel mutations (detection rate, 55.3%). Moreover, novel genotype-phenotype correlations were discovered, and phenotypic trends noted. Three cases are reported, including the identification of AHI1 as a novel candidate gene for no syndromic retinitis pigmentosa. Conclusion: This study revealed novel genotype-phenotype correlations, including a novel candidate gene, and identified 124 genetic defects within a cohort with IRD. The identification of novel genotype-phenotype correlations and the spectrum of mutations greatly enhance the current knowledge of IRD phenotypic and genotypic heterogeneity, which will assist both clinical diagnoses and personalized treatments of IRD patients.

Chromatic pupil responses. Preferential activation of the melanopsin-mediated versus outer photoreceptor-mediated pupil light reflex.

AUTHOR: R. Kardon, S. C. Anderson, T. G. Damarjian, E. M. Grace, E. Stone, and A. Kawasaki

To weight the rod-, cone-, and melanopsin-mediated activation of the retinal ganglion cells, which drive the pupil light reflex by varying the light stimulus wavelength, intensity, and duration. Experimental study. Forty-three subjects with normal eyes and 3 patients with neuroretina visual loss. A novel stimulus paradigm was developed using either a long wavelength (red) or short wavelength (blue) light given as a continuous Ganzfeld stimulus with stepwise increases over a 2 log-unit range. The pupillary movement before, during, and after the light stimulus was recorded in real time with an infrared illuminated video camera. The percent pupil contraction of the transient and sustained pupil response to a low- (1 cd/m (2)), medium- (10 cd/m (2)), and high-intensity (100 cd/m (2)) red- and blue-light stimulus was calculated for 1 eye of each subject. From the 43 normal eyes, median and 25th, 75th, 5th, and95th percentile values were obtained for each stimulus condition. In normal eyes at lower intensities, blue light evoked much greater pupil responses compared with red light when matched for photopic luminance. The transient pupil contraction was generally greater than the sustained contraction, and this disparity was greatest at the lowest light intensity and least apparent with bright (100 cd/m (2)) blue light. A patient with primarily rod dysfunction (nonrecordable scotopic electroretinogram) showed significantly reduced pupil responses to blue light at lower intensities. A patient with achromatopsia and an almost normal visual field showed selective reduction of the pupil response to red-light stimulation. A patient with ganglion cell dysfunction owing to anterior ischemic optic neuropathy demonstrated global loss of pupil responses to red and blue light in the affected eye. Pupil responses that differ as a function of light intensity and wavelength support the hypothesis that selected stimulus conditions can produce pupil responses that reflect phototransduction primarily mediated by rods, cones, or melanopsin. Use of chromatic pupil responses may be a novel way to diagnose and monitor diseases.

Huang investigated the genotype-phenotype correlation and mutation spectrum in a large cohort of patients with inherited retinal dystrophy (IRD), which is a prominent cause of blindness worldwide. The research aimed to unravel the complex genetic heterogeneity and understand the relationship between genotype and phenotype in IRD. Utilizing next-generation sequencing, specifically exome sequencing with a targeted panel of 164 established retinal disease genes, 88 potential genes, and 32 retina-specific microRNAs, the researchers analyzed 179 Chinese families affected by IRD. The study identified 124 mutations in known retinal disease genes, with 79 of them being unique, resulting in a detection rate of 55.3% across 99 unrelated patients. Additionally, the investigation uncovered previously unknown genotype-phenotype correlations and phenotypic trends, providing novel insights into the intricacies of IRD. Notably, a potential candidate gene was also discovered. These findings significantly enhance our understanding of the genotypic and phenotypic heterogeneity of IRD, offering valuable insights for improved clinical diagnosis and personalized care for IRD patients. The study underscores the importance of genotype phenotype associations in elucidating the underlying mechanisms of IRD and may have implications for targeted therapeutic interventions in the future.

R. Kardon, S. C. Anderson, T. G. Damarjian, E. M. Grace, E. Stone, and A. Kawasaki investigated chromatic pupil responses and the preference for melanopsin-mediated versus outer photoreceptor mediated pupil light reflex activation. The study aimed to understand how the activation of retinal ganglion cells, controlled by melanopsin, rods, and cones, influences the pupil light

reflex by adjusting the wavelength, power, and duration of the light stimulus. The researchers conducted experiments on 43 individuals with healthy eyes and three individuals with neuro-retinal vision loss. Pupillary movements were recorded using video cameras during continuous Ganzfeld stimulation with red and blue light at different intensities. The results showed that blue light elicited significantly higher pupil responses than red light, especially at lower intensities. The study also observed variations in pupil responses in patients with specific retinal conditions. The findings support the notion that pupil responses can reflect phototransduction mediated primarily by rods, cones, or melanopsin.

3. PROPOSED METHODOLOGY

The non-invasiveness is granted by adopting the proposed pupillometric method, which requires no specific patient preparations with drugs or collyriums. If com- pared with other standard diagnostic techniques, particularly, electrorheological test, in this case no electrodes need to be placed on the patient skin: this is particularly convenient when dealing with pediatric patients. Particularly, in younger children electrophysiological testing are usually per- formed in sedation, thus requiring a more complex clinical setting (i.e. availability of operating theatre together with anaesthesiologist). Chromatic pupillometry has been proven to be effective in diagnosis of RP.

Advantages System

1) High accuracy

2)High efficiency

PROJECT DESIGN

System Architecture

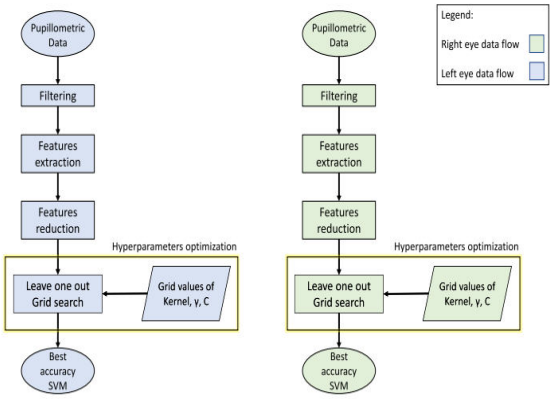

Figure 1: System Architecture

The main stages for the implementation of the RP classifier namely: import and pre-processing of the pupillary diameter signals, pupillary feature extraction and reduction, hyperparameters optimization and, finally, training of the supervised classifier. These stages are discussed in the following paragraphs.

Extreme Learning Machines (ELM):

ELM is a machine learning algorithm that belongs to the family of single-hidden layer feedforward neural networks (SLFN). Unlike traditional neural networks, ELM randomly initializes the weights between the input layer and the hidden layer and analytically determines the weights between the hidden layer and the output layer. ELM is known for its fast-learning speed and good generalization performance, making it suitable for large-scale data analysis and pattern recognition tasks.

Long Short-Term Memory (LSTM):

LSTM is a type of recurrent neural network (RNN) architecture that is designed to address the vanishing gradient problem in traditional RNNs. LSTM introduces memory cells and gating mechanisms to allow the network to learn and remember long-term dependencies in sequential data. It consists of input gates, forget gates, and output gates that control the flow of information through the network. LSTM networks have been successful in various tasks such as speech recognition, machine translation, and natural language processing, where the context and long-range dependencies are important.

Bidirectional Long Short-Term Memory (BiLSTM):

BiLSTM is an extension of the LSTM architecture that incorporates information from both past and future contexts. While LSTM processes the input sequence in a forward direction, BiLSTM also processes the sequence in reverse. By doing so, BiLSTM captures dependencies from both past and future states, allowing the model to have a more comprehensive understanding of the input sequence. This makes BiLSTM well-suited for tasks where context from both directions is important, such as speech recognition, sentiment analysis, and named entity recognition.

SIGNAL PRE-PROCESSING

A first preliminary stage of the CDSS is devoted to the analysis of the raw files, produced by the binocular pupillometer after each measurement session, for the export of the following relevant data:

- Patient ID
- Bilateral pupillary diameter signals related to each phase of the protocol
- Diagnosis, i.e., "Pathologic" or "Healthy", as performed by a clinical specialist.

4. EXPERIMENTAL ANALYSIS

The optimal combination of the SVM hyperparameters, returned by the data-driven tuning process, are reported in Tables 1 and 2, alongside the related classification accuracy achieved on the 30 available subjects.

Tables 3 and 4 summarize sensitivity, specificity and accuracy for the final ensemble model (schematized in Fig. 2).

The performance scores are derived by comparing the actual class of the subject as assigned by the physician -

with the class obtained by applying an OR logical operation to the two labels separately returned by the tuned SVMs for each eye. As expected, this strategy determines an increase in the overall sensitivity of the CDSS. It is worth to specifying that only one table is reported because both the linear and RBF kernel functions gave the same results in the ensemble logic.

Eye	Kernel	C	Accuracy
Right	Linear	100	86.7%
Left	Linear	1	83%

Table 1: Best Parameters for Left and Right Eye Features with Linear Kernel

Eye	Kernel	C	γ	Accuracy
Right	RBF	1000	0.001	80%
Left	RBF	1	0.1	90%

Table 2: Best Parameters for Left and Right Eye Features with RBF Kernel

Accuracy	Sensitivity	Specificity
86.7%	93.7%	78.6%

Table 3: Leave-One-Out Validation of the Ensemble Model: Performance

	Pathologic	Healthy
Pathologic	15	1
Healthy	3	11

Table 4: Leave-One-Out Validation of the Ensemble Model: Confusion Matrix

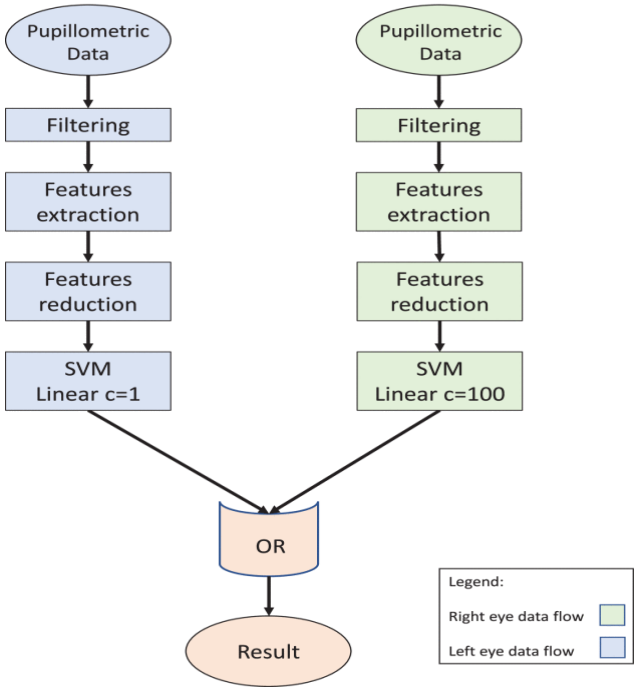

Fig 2: Decision support process.

5. CONCLUSION

This paper describes a new approach for supporting clinical decision for diagnosis of retinitis pigmentosa starting from analysis of pupil response to chromatic light stimuli in pediatric patients. The system was developed to clean artefacts, extract features and help the diagnosis of RP using a ML approach based on an ensemble model of two fine-tuned SVMs.

Performances were evaluated with a leave-one-out cross-validation, also used to identify the best combination of internal parameters of the SVM, separately for both the left and right eyes. The class assigned to each eye were combined in the end with an OR-like approach so as to maximize the overall sensitivity of the CDSS; the ensemble system achieved 84.6% accuracy, 93.7% sensitivity and 78.6% specificity. The small amount of data available for this work, calls for further tests with a larger data pool for validating the performance of the system.

Future scope includes testing the same approach with different devices. A problem that came out with great evidence, at the signal acquisition stage, is the frequent presence of movement artifacts. This is due to the particular shape of the device, together with the young age of the enrolled patients. Devices with different frame, including also systems based on smartphones, are going to be investigated.

Moreover, considering the duration of the whole acquisition protocol, the procedure would benefit of some systems to capture the attention of the young patient (and his/her sight).

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