Development of a Procedure for Detecting Dementia Symptoms Using Features in Differential Waveforms of the Pupil Light Reflex

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Abstract: A procedure for detecting dementia levels is developed using features of waveform shapes of the pupillary light reflex (PLR) in response to chromatic light pulses on either eye. Features of waveform shapes were extracted using a functional data analysis technique which measured the reactions of both eyes. In considering the physiological mechanism, differential waveform shapes were also analysed. The feature was extracted as a coefficient of B-spline basis functions of the waveforms. The feature sets of the differential waveform shapes for blue and red light pulses contributed to detection performance. Also, feature weights are used to represent PLR reaction mechanisms and differences in response to chromatic stimuli.

1 INTRODUCTION

Conventionally, the pupil light reflex (PLR) is based on ipRGC (intrinsically photosensitive retinal ganglion cell) systems which can be an index for the diagnosis of various types of diseases (Gamlin et al., 2007; Kawasaki and Kardon, 2007; Chougule et al., 2019; Kelbsch et al., 2019). In order to develop a biomarker of diseases, PLRs in response to chromatic stimuli have been observed and analysed (Nowak et al., 2020; Nowak et al., 2021; Nakayama et al., 2022; Nakayama et al., 2023b). In particular, the differential responses caused by problems with signal transfer by the optic nerve of each eye may provide clinical information such as the influence of dementia or Alzheimer's disease on the synchronisation of pupil reactions (McDougal and Gamlin, 2015; Chaitanuwong et al., 2023; Molitor et al., 2015; Nie et al., 2020). Asynchronicity of PLRs of both eyes shows some symptoms of the disease in the optic nerve system, as some factors may influence on PLRs, since most participants are elderly people (Nakayama et al., 2024a). In order to observe the disparity of both pupils, PLR measurements of both eyes using a light pulse to either eye may be useful (Nakayama et al., 2022; Nakayama et al., 2023b; Nakayama et al., 2024b). Another issue is the methodology of feature extraction of PLR waveforms, because the waveform shapes of PLRs may reflect the dynamics of physiological functions. However, overall waveform features have been used before, though detection performance for irregular responses was insufficient (Nowak et al., 2019). In order to improve performance significantly, a set of specific features of PLRs measured during the pupil constriction phase was introduced instead of the overall set of features. The remaining part of the waveform, composed of pupil reactions after the eye has recovered from constriction are often referred to as post-illumination pupil responses (PIPRs) in the diagnostic procedure. In considering the localised features of waveform shapes, an improved feature extraction procedure for entire waveform is required. A functional data analysis technique can be applied to waveforms of any length and waveform features including PLR waveforms can be extracted (Nakayama et al., 2024a). The benefit of this will be confirmed in this paper.

This paper examines the possibility of detection for dementia levels using differential features of waveform shapes of PLRs. In particular, the effectiveness of extracting features from an entire PLR waveform and introducing features of differentials of PLR waveforms is discussed. The following topics are addressed in this paper.

1. The features of waveform shapes, which are sum-

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mations and ratios of PLRs of both eyes, are extracted using a B-spline technique while either eye is irradiated in blue or red light pulse.

2. Classification performance of the level of dementia is examined using a combination of extracted features of PLRs

The following section of this paper consists of related works, where the method, classification analysis for patients and normal control group, and summary of the work are based on previous studies.

2 RELATED WORKS

Some clinical surveys measuring PLR reactions to chromatic light stimuli have been conducted since ipRGC was discovered (Gamlin et al., 2007; Kawasaki and Kardon, 2007; Chougule et al., 2019; Kelbsch et al., 2019). In addition to these studies, possible levels of dementia have also been measured using chromatic light pulse stimuli of the pupil (Molitor et al., 2015; Nie et al., 2020). Since the number of patients who can participate is limited, most analyses have been published as case studies. In due course, more systematic surveys were conducted, and additional analytical reports were published (Nakayama et al., 2022; Nakayama et al., 2023b). This survey consists of two sets of light irradiation, of the left and right eyes, as validation tests using previously studied data sets of left and right eye light pulses (Nakayama et al., 2022; Nakayama et al., 2023b). The ocular responses of each eye may differ, even though the same stimulus is provided simultaneously. The responses of either eye can be summarised as independent data sets when differential metrics are introduced (Nakayama et al., 2024b). In experimental surveys, the participation of patients is limited, and asymmetric responses can be used to compensate for the dearth of measured data.

However, in these previous studies the analyses employed a set of fixed feature points which were extracted during a large reaction to the light pulse (Nowak et al., 2020; Nowak et al., 2021). The overall features of PLR waveform shapes should be introduced, as mentioned in the introduction. One approach may be the extraction of feature of waveform shapes using a B-spline technique (Ramsay et al., 2009; López et al., 2022; Nakayama et al., 2024a), however an appropriate dimension reduction technique will be required in order to suppress the large number of dimensions of the features. The features of entire waveform shapes may be useful for the detailed analysis of time series data, and the temporal features can be compared for the feature selections. The possibility of patient detection using PLR waveform features should be examined. In most cases, B-spline is often employed as a basis function. Therefore, this work is based on this conventional procedure as the first step.

3 METHOD

The set of PLR data consiting pupillary responses to be analysed was surveyed in previous studies (Nakayama et al., 2022; Nakayama et al., 2023b), which measured 1 sec. chromatic light pulses (blue or red) to either eye during a 10 sec. period of observations. The participants were elderly people and included some patients with Alzheimer's disease (AD), mild cognitive impairment (MCI) and a normal control group (NC).

3.1 Experimental Procedure

3.1.1 Measurmement Protocols

Pupil diameters of each eye were measured for 10 sec. in a temporal darkened space under the following conditions (Nakayama et al., 2022). PLRs were measured during Conditions 2-5.

1. Condition 1: Observe static pupil oscillation without light pulses
2. Condition 2: Blue light pulses to the right eye
3. Condition 3: Blue light pulses to the left eye
4. Condition 4: Red light pulses to the right eye
5. Condition 5: Red light pulses to the left eye

The light stimulus is irradiated for one second during each session. The combination of the experimental conditions is fixed for all participants. In regards to each of the four light pulse irradiation conditions, the measured data is classified into sets for irradiation of the left and right eyes. Condition 1 is a set of common data for both eyes (Nakayama et al., 2024b).

The experimental procedure was approved by an ethics committee at Osaka Kawasaki Rehabilitation University.

3.1.2 Apparatus

Pupil diameters of both eyes were observed using a piece of specialised measuring equipment at 60Hz (URATANI, HITOMIRU). Light stimuli consisted of a blue light source (469nm, 14.3cd/m^2, 6.5lx) and a red light source (625nm, 12.3cd/m^2, 10.5lx).

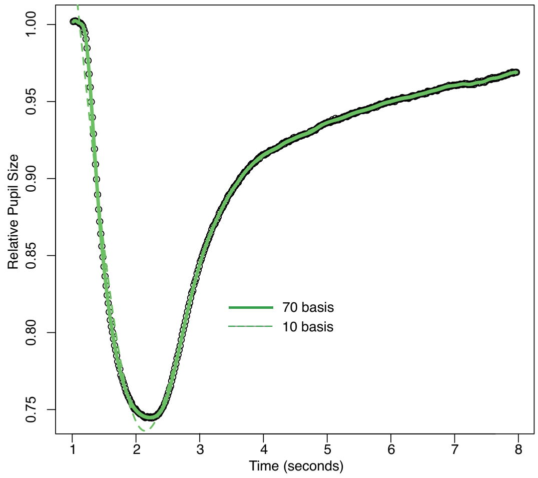

Figure 1: A summation signal of PLRs for blue light pulses.

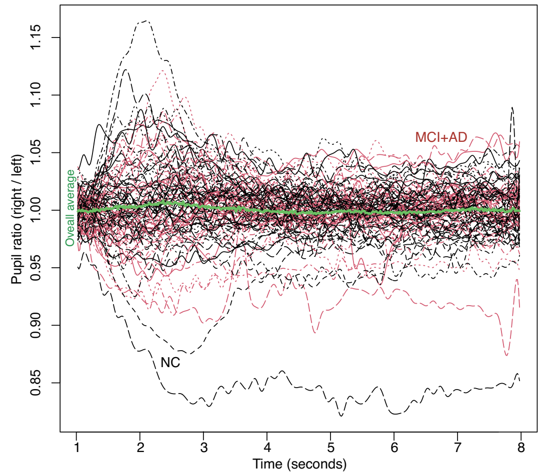

Figure 2: Individual differential signals of PLRs for blue light pulses.

3.1.3 Experimental Participants

101 elderly individuals were selected to take part in the experiment (Mean age : 78.5, SD : 8.9, F:66, M:35) (Nakayama et al., 2022; Nakayama et al., 2023a). Their cognitive functions were diagnosed by a clinical doctor and sorted into three levels using MMSE (Mini-Mental State Examination) scores (Tombaugh et al., 1996).

- AD: 32 (Mean age:83.0, SD:6.3, F:22, M:10).
- MCI: 9 (Mean age:82.1, SD:6.3, F:5, M:4).
- NC: 60 (Mean age:75.6, SD:9.2, F:38, M:22).

3.2 Analysis of Functional Data

Measured pupil sizes are summarised into sets for irradiation of the left and right eyes, forming two sets of data (the left and right eye data sets). Condition 1 is provided as a common control condition. Observed signals from both eyes are processed as summation of thr left and right eyes, and the ratios between the sizes for the left and right eyes right size/left size) are asynchronous measurements. All data are standardised using the initial level measurements made during the initial 1 sec. before irradiation. Also, the period of the final 2 sec. is eliminated in order to reduce the amount of data measured. Figure 1 shows the overall means of summation waveforms of the left eye responses to right eye blue light irradiation. The horizontal axis represents the time course, from 1 to 8 seconds. A waveform of pupil size shows pupil constrict, with dome delay, after 1 second blue light pulse (1-2sec.). The summation waveform is very smooth. This waveform can be represented using a B-spline basis function as a functional data analysis technique (Ramsay et al., 2009; López et al., 2022). When 70

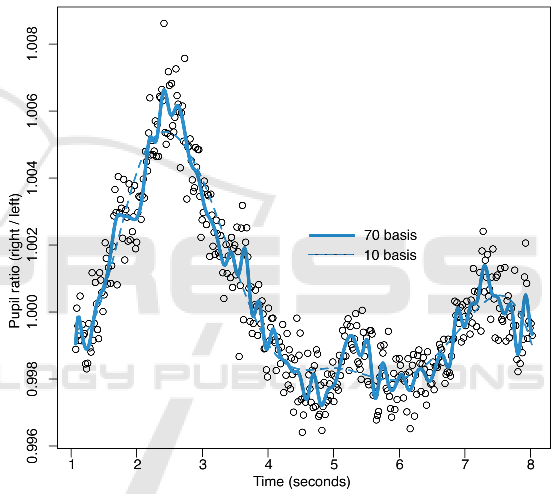

Figure 3: A differential signal of PLRs for blue light pulses.

basis functions are introduced (the solid line), the fit is much better than in the case of 10 basis functions (the dotted line), as shonwn in Figure 1. In this paper, a condition with 70 basis functions is selected for evaluating errors of reproduction and detection performances, as detailed in the following analysis.

The individual differential ratio of both eyes is illustrated in Figure 2. Most differential lines are connected around ratio=1, though some differences are observed around light pulses (1-3sec.) and at the end of the observation period (8 sec.). The red lines indicate patient cases (AD and MCI). A summation of these waveforms is illustrated in Figure 3, showing that even the changes in overall summation have not been smoothened. In this case, 70 B-spline basis functions are required to represent the waveform.

As an FDA technique, sets of coefficients of basis functions can be used to represent features of wave-

Table 1: Contingency table: Right trained / Left tested.

Participants	Classified		Total
	NC	MCI+AD	
NC	54	6	60
MCI+AD	24	17	41
Total	78	23	101

form shapes of PLRs or differential PLRs. These sets of features of PLR waveforms are used for classification of participants in the section which follows.

4 CLASSIFICATION RESULTS

Using the extracted features from waveform shapes and logistic regression functions, patients are classified as either patients (AD or MCI) or NC participants. A logistic function presents the probability of diagnosing patients using the set of features mentioned above. The waveform features are generated from waveform shapes, and measurement conditions such as using blue, red, or both colours of chromatic lights, can be combined. However, the number of dimensions of features increases even as the LASSO technique (Kawano et al., 2018) is introduced in order to select features which are significant.

In an evaluation of classification performance, cross validation of the irradiation of the right or left eye is introduced and another set of data of left and right eye measurements is used, for example, when the regression model is trained using the data set of the right eye and tested against the data set of the left eye. In comparison of performance using several combination of features of waveforms, the best performance obtained to date is from a combination of using a control condition, and differential ratios for blue and red light, for a total of 270 dimensions of features.

A contingency table classifying performance is summarised in Table 1. The horizontal column represents the classified results, and the vertical row shows the type of participant. Once again, the results present the classification of the data set of the left eye using a regression model trained with the data set of the right eye. In the results, 71 out of the 101 participants were classified correctly using a threshold 0.5, and the accuracy was 70%. In another regression model classification of the right eye, the accuracy was 65%. Though an improvement of detection performance is required, the differential ratios of irradiations using both blue and red light pulseses may indicate the existence of physiological impairment, which causes dementia.

Using the data set combination, detection occurs

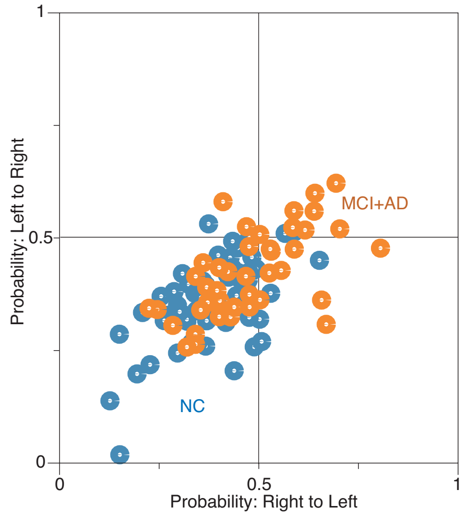

Figure 4: A differential signal of PLRs for blue light pulses.

Table 2: Contingency table using both detections.

Participants	Classified			Total
	NC	Either(+)	Both(+)	
NC	52	6	2	60
MCI+AD	22	11	8	41
Total	74	17	10	101

twice for each participant. are produced for each participant. These probabilities are summarised in Figure 4. The horizontal axis represents the probability of patients trained with the right eye data set and tested using the left eye data set, and the vertical axis represents probabilities of patients trained with the left eye data set and tested using the right eye data set. In the figure, the blue dots represent NC participants, and the orange dots represent MCI or AD patients. The threshold of 0.5 is represented by fine lines along the horizontal and vertical axes. The plots of many participants overlap in the centre of the graph.

The two procedures produce two probabilities, so participants are classified again using the logical OR of the two classification results. These results are summarised in Table 2. Using this procedure to merge the results, the number of patient detections increases slightly. However, overall accuracy remains at the same level such as 70% in the case mentioned above.

In order to evaluate the contribution of extracted waveform features, the feature values are summarised, as shown in Figure 5. The horizontal axis represents time such as a dimensional sequence, and the vertical axis represents the weight values. Mean weights of the three waveforms for control, blue, and red differentials of the data sets of the right and left eyes are summarised. The weights on both sides are almost the same. Regarding the changes in weights,

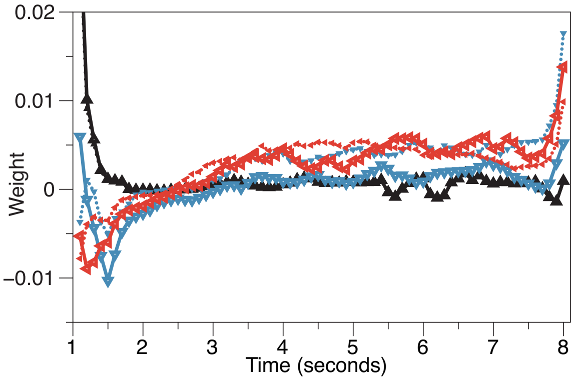

Figure 5: Comparison of coefficients of PLRs for control (black), and differentials for blue and red light pulses.

the amounts are relarively large during the light pulses and at the ends of the observations. There are some differences between blue and red light pulses. Also, the weights for red light pulses are maintained after the light pulse. As a phenomenon, post-illumination pupil response (PIPR) is observed in the case of red light irradiation. These differences may suggest that some weight patterns at the ends of the reaction observations show some increase. These results indicate that the most correct detections are accomplished by using the overall features of PLR waveform shapes.

Further feature selection and additional features of waveforms from around the irradiation of light pulses when constriction of the pupil does not occur may be required in order to improve performance. The factor of the basis function should be also evaluated to improve performance. In addition, MCI and AD detection performance will be examined. As the number of patients is limited, a different detection procedure will be required. A detailed analysis of performance improvements will be a subject of our further study.

5 SUMMARY

The hypothesis that pupillary light reflex (PLR) waveform shapes may provide feature metrics about patients with dementia was tested using a functional data analysis technique to extract features of overall waveforms. Detection performances of a clinical survey data consisting of PLRs of chromatic light pulses to either eye was evaluated. The features of differential waveform shapes of each eye contributed to their classification. The feature of waveform shapes also presented physiological features of PLRs of chromatic light pulses.

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