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Symptoms of Dementia in Elderly Persons using Waveform Features of Pupil Light Reflex

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Abstract. A procedure for detecting cognitive impairment in senior citizens is examined using pupil light reflex (PLR) to chromatic light pulses and a portable measuring system. PLRs of both eyes were measured using blue and red light pulses aimed at either of the two eyes. The symptoms of cognitive function impairment were evaluated using a conventional dementia test during clinical surveillance. The extracted features of observed PLR waveforms for each eye remained at a comparable level for every group of participants. Three factor scores were calculated from the features, and a classification procedure for determining the level of dementia in a subject was created using regression analysis. As a result, the contribution of factor scores for blue light pulses on both eyes according to a participant's age was confirmed.

Keywords: Pupil · Pupil Light Reflex · Alzheimer's disease · Feature extraction · Logistic regression.

1 Introduction

Symptoms of cognitive function impairment are used to diagnose Alzheimer's Disease (AD) and mild cognitive impairment (MCI). A major diagnostic procedure is the Mini-Mental State Examination (MMSE), which is based on a set of face-to-face clinical tests. These require participants to have sufficient communication skills, however. Therefore, a quicker and easier objective procedure should be developed using appropriate bio-makers. Pupillary responses are often observed to monitor mental activity as well as the pupil light reflex (PLR), which represents the dynamic characteristics of pupil behaviour [4, 25].

The study of conventional PLR activity suggests that as this activity represents the visual information processing of retinal stimuli and the ability to activate neural signal transfers [12, 5], it should be evaluated as an alternative means of diagnosing cognitive function impairment [26, 3]. Also, PLR responses based on Melanopsin ganglion cells [15, 21, 40] can be applied to the study of Aged Macular Disease (AMD) and AD [15, 21, 8], and the possibility of their use in diagnosing these diseases has been studied [29, 34, 32, 31]. A simple procedure to detect AMD and AD patients is required for medical and clinical staff who treat elderly people [33]. In a sense, a diagnostic procedure using ocular-motors may be an easy method, as it does not require verbal communication.

The authors have been conducting feasibility studies about how to conduct PLR observations at clinical institutions using a portable measuring system. During the current survey, additional elderly people were invited to participate, and their responses were analysed in order to examine the possibility of diagnostic prediction. Estimation performance and validity were evaluated. In this paper, the following points are addressed.

1. Features of PLRs for blue and red light pulses of the left and right eyes are compared, and the differences are extracted.
2. The ability of classifying participants as AD/MCI or normal control (NC) using MMSE scores and PLR features.
3. The contribution of the participant's age is also examined.
4. Procedures for predicting the performance of participants with AD or MCI are developed and evaluated.

The reminder of the paper is structured as follows. Section 2 reviews previous and related work. Section 3 introduces methodologies of experimental observation, such as feature characteristics of PLRs. Experimental results and regression analysis are detailed in Section 4. The Discussion and Conclusion of the results are summarised in the following sections.

2 Related Work

2.1 Diagnostic for Alzheimer's Disease (AD)

The study of Alzheimer's disease in clinical and pathological approaches has a long history [10, 6]. Early diagnosis and appropriate treatment of the disease are required [35, 36]. The diagnostic and testing procedures currently in use have been studied and their accuracy has often been discussed [2, 7]. Though various clinical aspects of AD patients or patients with dementia, such as mild cognitive impairment (MCI) have been studied, the typical features which present AD symptoms have not yet been examined. Major diagnostic tools are almost always based on clinical and pathological measurement such as brain imaging and certain biomarkers [23, 27] while clinical surveillance is frequently preferred using medical consultations.

Even so, clinical doctors have to diagnose using observations such as the MMSE (Mini-Mental State Examination) question inventory [11] or other procedures. As MMSE is used by observers to mark conditions during subject observation, the validity of the results depends on the activity of the targeted participant. Some improved consultation procedures are also being developed to enhance accuracy [38].

However, the diagnostic procedure is based on clinical observations using verbal communication. If the participants have sensor impairments, it may not be possible to conduct these types of tests. In another procedural approach to diagnosis, participant's behavioural responses, acoustic features of their spoken voice [17, 41, 24], gait features [1], and oculo-motors [32, 31] have been analysed technically. Some new measurements using vision functions are also being studied to introduce new diagnostic approaches [39, 26, 8].

In particular, eye pupil reaction such as the pupil light reflex (PLR) is often referred to as one of the bio-markers for detecting AD patients since melanopsin related ganglion cells (ipRGC) have been discovered [21, 14]. The detailed mechanism of the PLR and diagnostic procedures for detecting cognitive impairment based on ipRGCs and ipRGC-based PLRs have been studied [40, 8]. Regarding the possibility of diagnosing AD patients, most conventional observations were conducted using a flash light and employing white light [13] of longer wavelengths, such as 585nm [5], 820nm [13], or other wavelengths [14, 8]. The observation procedures and the characteristics extracted from PLRs have been discussed regularly. Some characteristics of PLR waveforms are extracted and compared with light wavelengths of colours such as blue or red [9, 42] as suggested in previous works [21, 20, 18]. Though some PLR-based diagnostic prediction procedure using features of the waveforms are proposed [32, 31], key features of PLRs and the appropriate procedures have not yet been extracted. As the previous studies have produced various successful assessments, feature extraction approaches to ipRGC based PLRs will be discussed in this work, with the most appropriate observation procedure for a PLR based diagnostic prediction procedures also being considered.

2.2 PLR Mechanism

Most of these procedures are based on the performance of signal transfer from retinal ganglion cells to the pretectal area via the optic chiasm, while the Edinger-Westphal (E-W) Nucleus also plays a major role in PLR [28, 42, 22]. Some impairment of the transfer path and the E-W Nucleus, such as neuronal loss, may influence AD patients [37, 8]. Overall performance of the synaptic signal transfer may not be evaluated individually.

In the case of a proposed diagnostic procedure for Aged-Related Macular Disease (AMD) which also influences synaptic signal transfer, asynchronous PLR appearances between the eyes was focused on and evaluated quantitatively using waveform features [29]. It may be possible to consider using this type of experimental protocol to assess procedures for detecting symptoms in AD patients. These two diseases influence the extent of retinal damage or the contribution of photoreceptors and because they serve as pathways for signal transfer [22], they can be used as a means of simplifying AMD diagnosis [29]. In regards to the diagnostic issues, observation of these conditions should be focused on using the responses of each eye, even when the reactions of both eyes are measured synchronously. In most studies, the difference between the eyes is not considered since both pupils and eyes are thought of as changing synchronously, such as during consensual light response [42]. Also, similar processing can even be employed during diagnostic procedures which use PLR responses. This aspect should be considered using binocular synchronous observation in the analysis. For example, the following experiment may be introduced so that the PLR responses of both eyes are evaluated separately when either eye is irradiated by short or long wavelength light pulses. Therefore, the performance of the retinal signal transfer pathway of either eye and the reflex response signal transfer pathways of both eyes could be evaluated when a light pulse is presented to either eye. The following experiment introduces binocular pupillary observations in response to light pulses on either eye as a means of inducing chromatic stimulus.

2.3 Participant Factor

Most AD patients and persons presenting symptoms of dementia, including MCI, are elderly and almost all are receiving medication to treat health problems. In addition to individual differences including cognitive performance [16], pupil size generally decreases with age due to senile miosis. Cataract of the lens may also influence sensitivity to PLRs. In order to create a detection procedure for AD patients, a comparison of patients and normal control (NC) subjects is required initially. Even NC persons may exert some influence over their PLR responses.

Fundamentally, recruiting AD and MCI patient volunteers may not be easy once the experimental procedure is ethically approved [32]. Even a clinical doctor may only ask a limited number of candidates to participate. Therefore, most experiments have to be conducted by employing a small number of patients. If the number of participants grows, the condition of each individual with dementia and their health issues should be considered carefully during the evaluation of the results of experiments. Also, measured pupillary data should be carefully processed since participants may not be able to control blink and eyelid lift during observation. At minimum, the age and cognitive ability test scores of participants are required, but the deviations caused by individual differences need to be considered.

In order to invite elderly people to participate in an observation experiment which contained a balance between patients and NC group participants, family members of patients were encouraged to join so that a sufficient number of observations of additional elderly people could be made.

3 Method

Pupil light reflex was observed in senior citizens who may be AD patients, pseudo-positive participants, or have no cognitive impairment i.e., normal.

3.1 Experimental Procedure

Participants were introduced to a temporary dark space, where the 5 following experimental sessions were conducted for 10 seconds each.

Fig. 1. Equipment to observe pupillary changes

1. Condition1: Control session without light pulses
2. Condition2: Blue light pulse to the right eye
3. Condition3: Blue light pulse to the left eye
4. Condition4: Red light pulse to the right eye
5. Condition5: Red light pulse to the left eye

The experiment is designed to study the influence of light pulses on synaptic connections between both eyes in response to light pulses to either eye. Light pulses transfer from retinal ganglion cells on the irradiated eye to sphincters of both eyes via the Edinger-Westphal Nucleus, as mentioned above. The processes of miosis and restoration were observed in all 4 sessions. A short relaxation break was inserted between each session.

The size of pupil responses were measured in pixels at 60Hz using equipment with blue and red light sources, as shown in Figure 1 (URATANI, HITOMIRU). The light sources were blue (469nm, 14.3cd/m^2, 6.5lx) and red (625nm, 12.3cd/m^2, 10.5lx). The size of both pupils during all conditions was measured. Blink artefacts were removed manually after measurement.

The experiment was conducted by a clinical physician at a medical institution, and the procedure was approved by an ethics committee of Osaka Kawasaki Rehabilitation University.

3.2 Participants

Valid data was obtained from 101 participants, of which 66 were female and 35 were male. Their mean age was 78.5 and the SD (standard deviation) was 8.9 years. Participants at a medical institute were selected, and an MMSE test was conducted. The results were classified into three groups according to MMSE scores. These were AD (Alzheimer's disease, with MMSE<=23), MCI (Mild cognitive impairment, with MMSE<=27) and others, whose conditions was NC (Normal Control). The distribution was as follows:

- AD: 31 (F:21, M:10), Mean age: 83.0, SD: 6.3 years.
- MCI: 9 (F:5, M:4), Mean age: 82.1, SD: 6.3 years.
- NC: 61 (F:40, M:21), Mean age: 75.6, SD: 9.2 years.

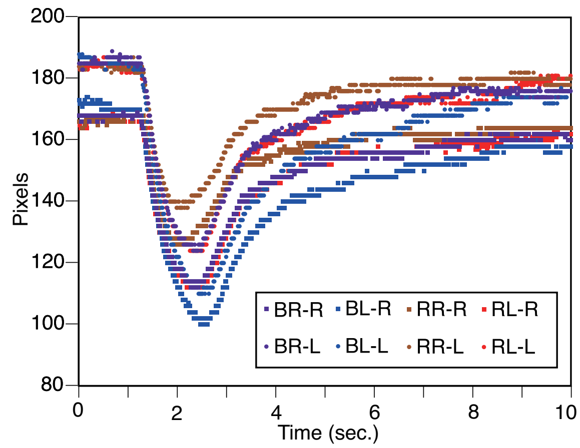

Fig. 2. Examples of PLR of both eyes for four conditions (NC participant, 76yo, M), categories:[light colour][irradiated eye]-[observed eye]

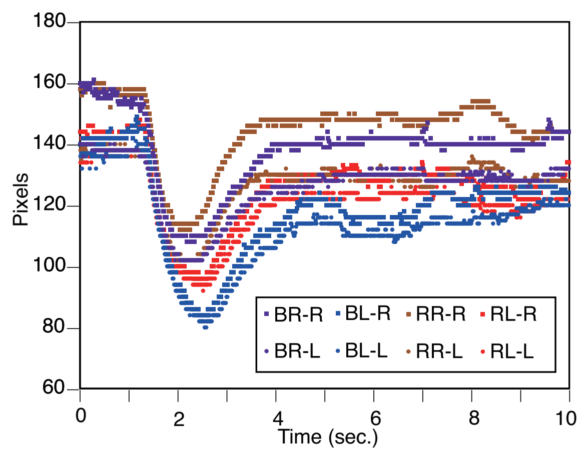

Fig. 3. Examples of PLR of both eyes for four conditions (AD participant, 87yo, F), categories:[light colour][irradiated eye]-[observed eye]

As the age of participants may influence their condition, four age levels were created: less than 66 years old (0), 66-75 years old (1), 76-85 years old (2), above 85 years old (3). Though participants were elderly and might have some health problems, these points were not considered during the following analysis.

Table 1. Features of PLR

Variables	Definitions
RA	Relative Amplitude of miosis
t_min	Time at minimum size
diff_min	Minimum differential of size
t_diff_min	Time at minimum differential
diff_max	Maximum differential of size
t_diff_max	Time at maximum differential
diff2_min	Minimum acceleration
t_diff2_min	Time at minimum acceleration
diff2_max	Maximum acceleration
t_diff2_max	Time at maximum acceleration

4 Results

4.1 PLR Waveforms

An example of PLR waveforms for a NC participant is shown in Figure 2. The horizontal axis represents time, and the vertical axis represents pupil size in pixels for the experimental conditions 2∼5. There are some differences in pupil size between the left and right eyes at the initial point. The legend "BR-R" means that Right pupil response when Blue light irradiates the Right eye, and also "RL-R" means that Right pupil response when Red light irradiates the Left eye. Also, levels of contraction are different between conditions, as in the previous work which presented PLR responses to blue or red light pulses [21]. Another example of an AD patient is shown in Figure 3. Some typical features are observed, such as deviation during the restoration process after constriction. Several features of waveforms were extracted in order to compare groups of participants in relation to the previous study [31], as shown in Table 1.

The first hypothesis is that there is a feature difference between the left and right eyes when light pulses are directed at either eye. The hypothesis was examined using a t-test of features of both eyes, such as between the irradiated eye and the non-irradiated eye. The features were extracted from standardised waveforms in order to reduce the potential differences.

In the results of the test, there are no significant differences in any of the features. There were a few exceptions, but the results did not coincide with the results of either colour of light pulse.

4.2 Regression Analysis based on Factor Scores

Since every feature includes measurement errors and individual differences, the latent factors are extracted using factor analysis according to the method used in the previous study [31].

The results of factor analysis are shown as a factor loading matrix in Table 2. In this paper, three factors are employed, and the overall contribution ratio of

Table 2. Factor loading matrix for PLR features

Variables	Factor1	Factor2	Factor3
diff_min	**0.87**	-.13	0.09
diff2_min	**0.76**	0.06	0.16
diff2_max	**-.83**	-.17	0.22
diff_max	-.36	0.08	0.15
RA	-.24	**0.78**	-.09
t_min	0.22	**0.73**	0.14
t_diff2_min	-.13	-.00	**0.49**
t_diff_min	-.05	-.03	0.36
t_diff_max	-.11	0.23	0.36
t_diff2_max	0.06	0.07	0.30

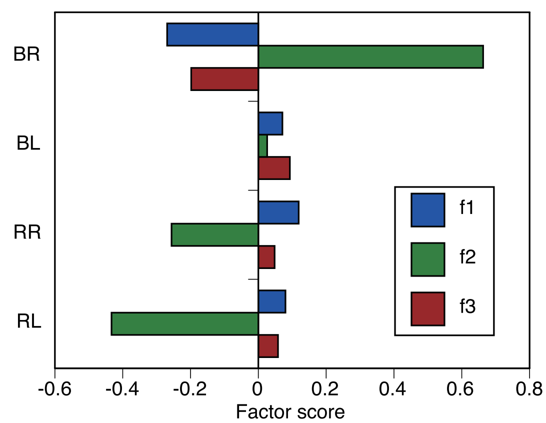

Fig. 4. Comparison of factor scores between stimuli (f1∼f3: factor scores for factors 1∼3)

the factors is 45.5%. Factor 1 represents the differential rate and acceleration of pupillary change, Factor 2 represents the features of contraction such as relative amplitude and its time, and Factor 3 represents the times for the differential rates and acceleration, as mentioned in Factor 1.

Three factor scores are calculated using the factor loading matrix. When the scores of both eyes are compared, there are also no significant differences.

The factor scores for experimental conditions are summarised and compared in Figure 4. Changes in Factor-2 scores suggest a continuous decrease according to the experimental conditions. Also, there are significant differences in the three factor scores for blue and red stimuli. Within each colour stimulus condition, there are significant differences in the three factor scores for blue light pulses, and significant differences in Factor-2 scores for red light pulses ($t(402) = 2.13, p < 0.05$). The differences between sessions using the same colour condition should

Table 3. Prediction models using factor scores of PLRs

Model	Variables	AUC
1	9 factor scores	0.77
2	9 factor scores + age group	0.84
3	9 factor scores + age	0.84
4	Selected variables: 5 factor scores + age group	0.84

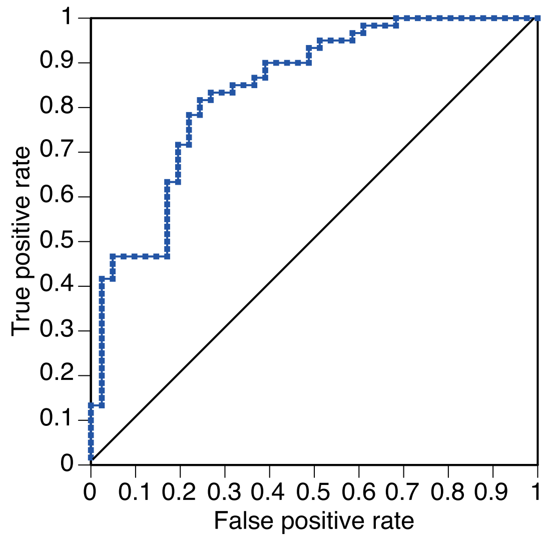

Fig. 5. ROC for Model 2 (AUC=0.84)

be considered, and in particular the differences for blue light should be evaluated separately.

In addition, the factor of age level on factor scores is examined using two-way ANOVA of participant groups and age levels. Though the factor for the participant groups is not significant, the factor for age level is significant for Factor-1 scores ($F(3, 801) = 19.9, p < 0.01$), and the interaction between the two factors (age and participant group) is also significant ($F(2, 801) = 9.4, p < 0.01$). Therefore, the factor of age may affect the differential and the acceleration of pupillary change, as presented in Factor-1 scores.

The influence of a subject's level of dementia on PLR features was not confirmed in the above analysis. The factors of stimulus light wavelength and the age of the patient were significant and are the major components of the deviation. In order to examine the effectiveness of the extracted features for a prediction of cognitive function impairment, an estimation procedure using a logistic analysis which had been introduced in a previous study [31] was conducted. Here, both MCI and AD patients are merged as the "AD+MCI" group since the number of MCI participants is limited. The probability of cognitive im-

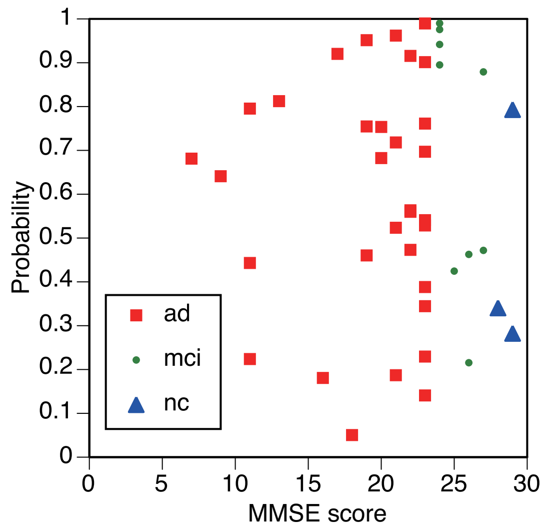

Fig. 6. Relationship between MMSE scores and computed probabilities

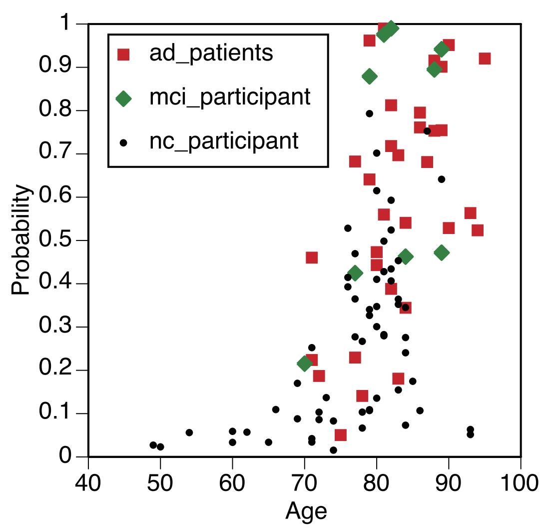

Fig. 7. Change in probability according to participant's age

pairment is calculated using factor scores for each participant. As there are no significant differences between eyes, averaged features of responses of both eyes are employed. In considering the differences between session stimuli, two sets of features for blue light conditions and averaged features for red light conditions are introduced, for a total of 9 variables altogether.

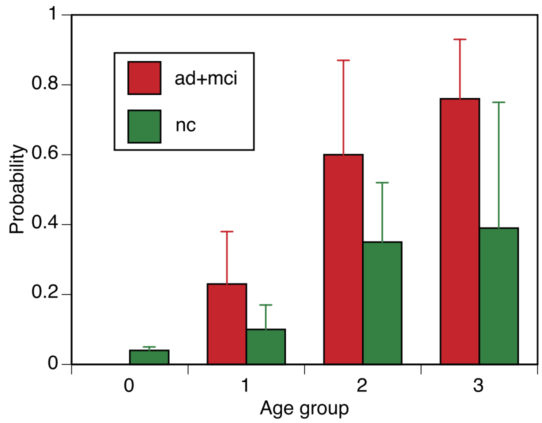

Fig. 8. Comparison of mean probabilities between AD+MCI and NC groups

Table 3 shows a summary of several prediction models and AUC (Area under the Curve) as an index of accuracy of binary classification for a ROC (Receiver Operating Characteristic Curve). Since the threshold for classification may depend on the diagnostic policy, such as reducing the False positive rate, accuracy is evaluated using AUC. An example of ROC for Model 2 is illustrated in Figure 5. Model 1 consists of 9 factor scores, Models 2 and 3 include age level or age. Model 4 employs significant contributing variables using a step-wise selection technique. Participant's age information aids classification performance.

Probabilities for the classification of cognitive impairment based on Model-2 are calculated, and the relationships between MMSE scores and the probabilities are summarised in Figure 6. The horizontal axis represents MMSE scores, and the vertical axis represents probability. Participants who were tested using MMSE are plotted in the figure according to their participant group, AD, MCI or NC. Confirmation of the contribution of a participant's age is shown in Figure 7, where the horizontal axis represents age. In this figure, cognitive impairment can be observed in subjects over 70 years old, and the probability increases markedly from around 70 onward. When the threshold for AD+MCI is set to 0.5, 80 percent of participants are classified correctly. The AUC is 0.84 as shown in Table 3.

Mean probabilities for the groups of AD+MCI and NC by age level are summarised in Figure 8, in order to evaluate the contribution of age level. Overall, mean probabilities increase with age level. In particular, the probability of AD+MCI increases over age 75, while mean probability of NC remains under 0.5. Model-4 in Table 3 was generated using a variable selection procedure. All 5 selected variables are factor scores for blue light pulses during two test sessions, and factor scores for red light pulses were not used. The AUC fitting index is comparable with the values of the other functions. This suggests the possibility that prediction can be made using responses to blue light pulses. A more detailed examination of this topic will be summarised in the following discussion section.

Table 4. Correlation coefficients for PLR waveforms between left and right eyes

Condition	1.0-2.5s	2.5-3.5s	3.5-10s	0.0-10s
BR:NC	0.99	0.98	**0.84**	0.97
BR:MCI+AD	0.99	0.97	**0.87**	0.97
BL:NC	1.00	0.99	**0.90**	0.98
BL:MCI+AD	1.00	0.99	**0.85**	0.97
RR:NC	0.99	0.97	**0.82**	0.96
RR:MCI+AD	0.99	0.96	**0.73**	0.97
RL:NC	0.99	0.96	**0.83**	0.96
RL:MCI+AD	0.99	0.96	**0.78**	0.96

5 Discussion

In the first hypothesis, cognitive impairment may be affected by the influence of the oculomotor nerve, which connects retinal ganglion cells to the pretectal area on the synaptic path. However, no significant differences in the extracted features were observed during several chromatic light pulses, though there were some differences between the experimental sessions, as shown in Figure 2. One of the possible reasons is the dependence on the accuracy of measurement, because feature extraction is based on point estimation. In particular, the small pupils of senior citizens may influence the measurement of temporal change of pupil size. Another problem may be that the extracted features focused on the constriction phase of PLRs without allowing for the restoration phase which follows. The difference in PLR between the left and right eyes should be measured carefully in considering the above points. During the main analysis, the AD+MCI group was set as the specific target for prediction. As a diagnostic application, the level of cognitive impairment needs to be able to be estimated using features of PLRs if it is to be effective. If it is possible, AD and MCI should be classified using weighted levels.

The factor scores for blue but not red light pulses were selected once more for use in a regression model, following a step-wise procedure. The dominance of blue light pulses for prediction was confirmed in a previous study [32, 31]. The possible reason for this may be based on the first hypothesis, which could not be confirmed according to the above evaluation, however. Therefore, a more detailed analysis needs to be conducted.

During the above waveform analyses, most features of both eyes were extracted from the constriction phase between 1.0 and 2.5s. As the initial hypothesis states, the differences between eyes, such as a direct-irradiated eye and a non-irradiated eye, was examined using a statistical mean differential test. In the results, there was no significant difference and the hypothesis was rejected. However, some differences in waveform shapes are observed in Figure 3, which illustrates the responses of an AD patient. Here, a more detailed analysis is tried using a simple mutual correlation analysis of two PLR waveforms for the left and right eyes. If the two eyes react synchronously, the correlation coefficient approaches 1. In considering the reaction phases such as constriction and the two stages of restoration, correlation coefficients are calculated and summarised across three phases for each stimulus condition in Table 4.

The overall correlation coefficients are presented in the right hand column, and nearly all approach the value of 1 (0.96∼0.98). During the initial phases (1.0∼2.5s and 2.5∼3.5s), the coefficients approach 1 since the dynamical reaction occurred simultaneously during constriction and early restoration phases. The coefficients decrease to less than 0.9 during late restoration phase (3.5∼10s), however. These coefficients suggest asynchronous responses between the two eyes. In particular, coefficients for MCI-AD participants are less than 0.8 when red light pulses are used. This suggests that differences in response of some patients may have occurred as part of the conventional light response mechanism. Though pupil responses during the second stage of restoration are studied as a post-illumination pupil response (PIPR) [19, 42], the synchronicity between the two eyes is not discussed sufficiently. As the phase difference appeared after the constriction phase, the reaction mechanism should be discussed carefully once more if the internal information processing for single eye irradiation with short and long wavelength light influenced responses. In regards to the hypothesis in this work, the details of this phenomenon could be resolved by referring to previous studies. Also, waveform features for the late restoration phase should be considered in the diagnostic procedure.

In addition to the above issues, there are some obvious limitations to this study. The first point is the accuracy of classification of patients. During the examination, the diagnostic category is only based on MMSE scores measured during consultations with a medical doctor. The degree of disease progress should be evaluated objectively. Also, the NC group may include some people who are patients. In this study, other metrics of cognitive functional ability have been observed, such as VSRAD (Voxel-based Specific Regional analysis system for Alzheimer's Disease), HDS-R (Hasegawa's Dementia Scale-Revised) and MoCA-J (a Japanese version of the Montreal Cognitive Assessment test). The development of an alternative diagnostic procedure which considers the level of cognitive function together with these metrics will be a subject of our further study. Even the design of the experimental conditions may have been insufficient. PLR responses were only observed for 10 seconds under certain conditions following a low intensity 1 second light pulse. Usually, observations should be conducted using at least two levels of light intensity. The second restoration phase after light pulse needs to be recorded for over 30 seconds in order to properly examine pupillary dynamics.

A revised experimental design which considers these limitations should be discussed. This will also be a subject of our further studies.

6 Conclusion

A procedure for detecting the level of cognitive impairment of senior citizens is examined using pupil light reflex (PLR) for chromatic light pulses and portable measuring equipment. Features of PLRs are compared between blue and red light pulses.

1. PLRs between left and right eyes are compared when light pulses are directed at either eye. In addition, the latent factor scores of PLR features are also extracted. There are no significant differences in features and factor scores between the left and right eyes, however.
2. Factor scores and participant's ages were analysed in order to classify individuals into groups such as AD+MCI and NC. Participant's age information contributed to classification of the groups. During the regression analysis using a variable selection procedure, factor scores for blue light pulses were extracted. PLRs for blue light pulses are key to accurate prediction.

As stated above, a more accurate prediction procedure and improvement of the method of analysis of the response mechanisms will be subjects of our further study.

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