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Detecting Symptoms of Dementia in Elderly Persons using 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) for chromatic light pulse and a portable measuring system. Features of PLRs of blue and red light pulses are compared. PLRs of elderly subjects were studied in order to develop a procedure for detection of the symptoms of cognitive function impairment using a dementia evaluation test. PLRs of both eyes were measured using blue and red light pulses aimed at either of the two eyes. The features of PLR waveforms for each eye were remained in comparable level for every group of participant. 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 according to a participant's age was confirmed.**

***Index Terms*—Pupil, Pupil Light Reflex, Alzheimer's disease, feature extraction, logistic regression**

I. 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 procedures should be developed.

The study of conventional pupil light reflex (PLR) activity [1], [2] suggests that as this activity represents to visual information processing of retinal stimuli and the ability to activate neural signal transfers, it should be evaluated as an alternative means of diagnosing cognitive function impairment [3], [4]. Also, PLR responses based on Melanopsin ganglion cells [5], [6], [7] can be applied to the study of aged macular disease (AMD) and AD [5], [6], [8], and the possibility of their use in diagnosing these diseases has been studied [9], [10], [11], [12] A simple procedure to detect AMD and AD patients is required for medical and clinical staff who treat elderly people [13]. In a sense, a diagnostic procedure using ocular-motors may be an easy way, as it does not require verbal communication.

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The authors have been conducting feasibility studies about conducting PLR observations using a portable measuring system at clinical institutions. During the current survey, additional elderly people were invited to participate and their responses were analyzed. 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 score and PLR features.
3) The contribution of the participant's age is also examined.
4) Prediction performances of participants with AD or MCI procedures are developed and evaluated.

II. 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.

A. Stimuli

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

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 [14]. The processes of miosis and restoration were observed in all 4 session. A short break to be relax was inserted between each session.

B. Procedure

The size in pixels of pupil responses were measured at 60Hz using an equipment with blue and red light source as shown

Fig. 1. Equipment to observe pupillary changes

TABLE I
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

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). Both pupil sizes were measured over all conditions. Blink artifacts were removed manually after the measurement.

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

C. Participants

The valid data was obtained from 101 participants, 66 females and 35 males. Their mean age was 78.5 and the SD (standard deviation) was 8.9 years. Participants were selected at a medical institute and 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.

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), higher than 85 years old (3). Though participants were older persons who might have some health problems, these points were not considered in the following analysis.

III. RESULTS

A. 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 to Right eye, and also "RL-R" means that Right pupil response when Red light irradiates to 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 [6]. Another example of an AD patient is shown in Figure 3. Some typical features are observed such as deviation during the restoration process after the constriction. Several features of waveforms were extracted in order to compare groups of participants in relation to the previous study [12] as shown in Table I.

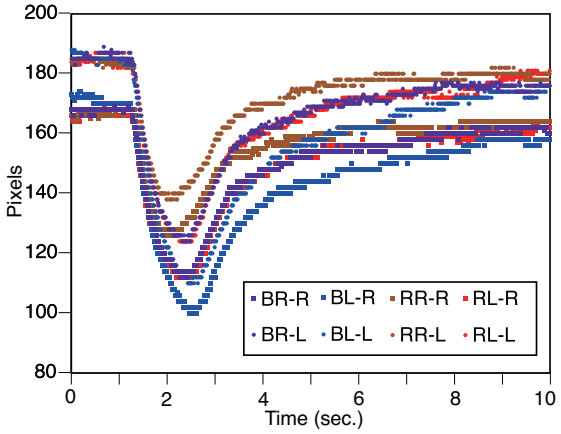

Fig. 2. Examples of PLR of both eyes for four conditions (NC participant, 76yo, M), categories:[light color][irradiated eye]-[observed eye]

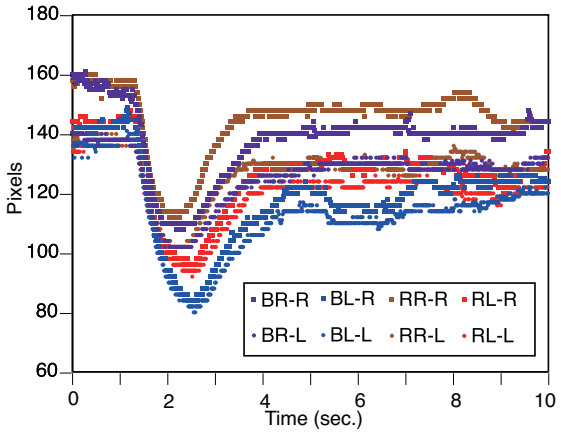

Fig. 3. Examples of PLR of both eyes for four conditions (AD participant, 87yo, F), categories:[light color][irradiated eye]-[observed eye]

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 irradiated eye and non-irradiated eye. The features were extracted from standardized waveforms in order to reduce the potential differences.

TABLE II
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

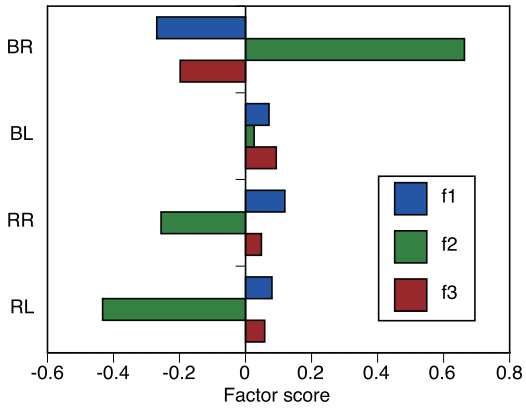

Fig. 4. Comparison of factor scores between stimuli (f1∼f3: factor scores for Factor 1∼3)

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.

B. Factor analysis and 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 [12].

The results of factor analysis are shown as a factor loading matrix in Table II. In this paper, three factors are employed, and the overall contribution ratio of 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 it's 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 these scores of both eyes are compared, there are also no significant differences.

The factor scores for experimental conditions are summarized 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 of blue and red stimuli. Within a 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 be considered, 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.

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 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 [12] 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 impairment 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.

Table III 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 a threshold for the classification may depend on the diagnostic policy such as reducing False positive rate, the 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 stepwise 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 summarized in Figure 6. The horizontal axis represents MMSE scores, and the

TABLE III
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

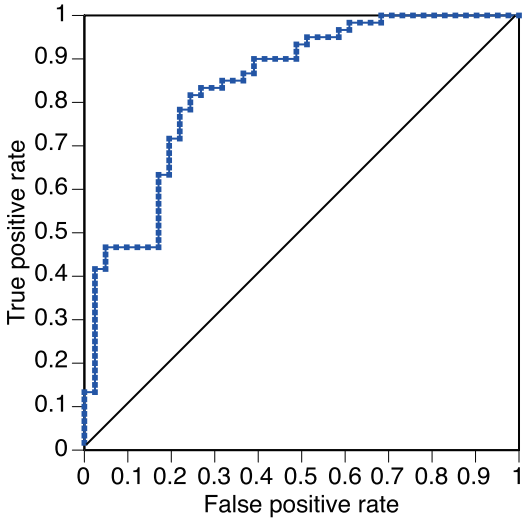

Fig. 5. ROC for Model 2 (AUC=0.84)

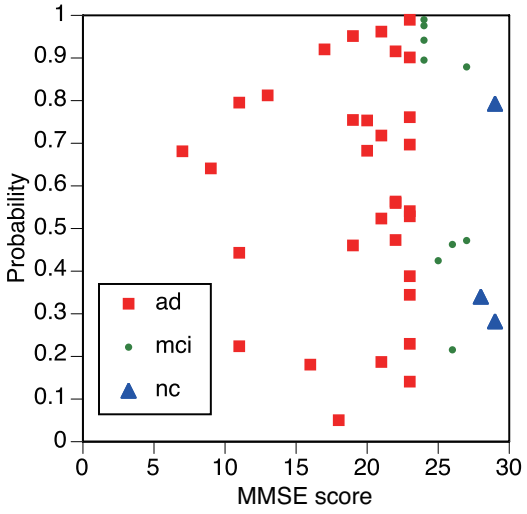

Fig. 6. Relationship between MMSE scores and computed probabilities

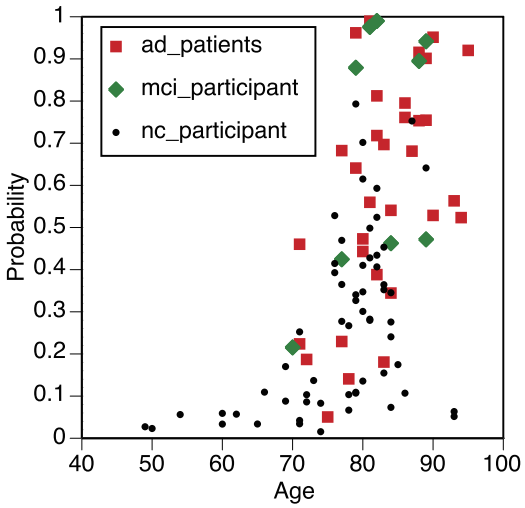

Fig. 7. Change in probabilities according to participant's age

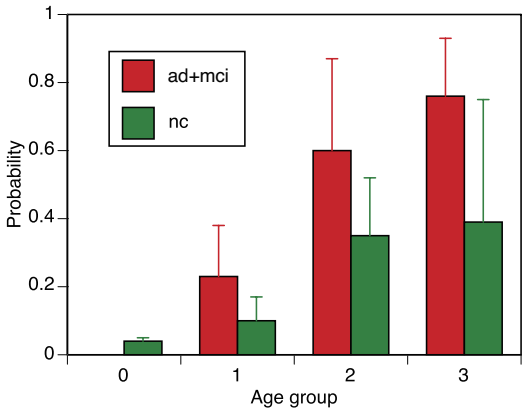

Fig. 8. Comparison of mean probabilities between AD+MCI and NC groups

vertical axis represents the 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 the age. In this figure, cognitive impairment can be observed in subjects over 70 years old, and the probability increases markedly from around 70 onwards. 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 III.

Mean probabilities for the groups of AD+MCI and NC by age level are summarized 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.

C. *Variable selection of the regression function*

Model-4 in Table III 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 fitting index AUC is comparable with the values of the other functions. This suggests the possibility that prediction can be made using responses to blue light pulses. More detailed points regarding this will be summarized in the following discussion section.

IV. 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 PLR difference between the left and right eyes should be measured carefully in considering the above points. During the main analysis, AD+MCI group was set to the specific target of prediction. As a diagnostic application, the level of cognitive impairment need to be able to be estimated using features of PLRs if it is to be would be effective. If it were 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 stepwise procedure. The dominance of blue light pulses for the prediction was confirmed in a previous study [11], [12]. 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.

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 (Japanese version of Montreal Cognitive Assessment). The development of an alternative diagnostic procedure which considers the level of cognitive functioning together with these metrics will be a subject of our further study.

V. Summary

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

1) PLRs are compared between left and right eyes when light pulse provides 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 analyzed 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.

A more accurate prediction procedure and method of analysis of the response mechanisms will be subjects of our further study.

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