Communication Papers of the 18th Conference on Computer Science and Intelligence Systems pp. 201–207
DOI: 10.15439/2023F3416
ISSN 2300-5963 ACSIS, Vol. 37

# Using Features of PLRs to Chromatic Light Pulse Irradiations of Either Eye to Detect Dementia in Elderly Persons

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***Abstract*—A procedure for detecting symptoms of dementia was developed using waveform features of pupil light reflexes (PLR) of both eyes, in response to blue or red light pulses directed toward either eye. The experiment was conducted using elderly people with Alzheimer's disease, mild cognitive impairment, and a normal control group who were not patients. This paper focuses on the differences between the features of irradiated and non-irradiated eyes, and two combined metrics were produced in addition to the three factor scores in our previous work. The level of dementia was estimated using two regression functions with the extracted features. The performance of the procedure developed was evaluated using two sets of data, and its validity was confirmed.**

***Index Terms*—Pupil, Pupil Light Reflex, Alzheimer's disease, feature extraction, both eyes**

## I. Introduction

One major clinical assessment for dementia is a medical diagnosis known as the Mini-Mental State Examination (MMSE). The rating classifies participants into groups with Alzheimer's Disease (AD) or mild cognitive impairment (MCI). However, as this clinical test is based on face-to-face surveillance, sufficient verbal communication is required. The authors have been trying to develop a metric using reactions to pupil light reflex (PLR) activity in order to improve the early clinical diagnostic procedure [1], [2], [3]. Approaches using PLR have been studied during previous research [4], [5], [6], [7]. In particular, PLR responses based on Melanopsin ganglion cells can be an index for the detection of dementia symptoms [8], [9], [10], [11].

Some of the previous studies have suggested that dementia may be influenced by the optic nerve which transfers light detection signals from the retina to a unit of the Edinger-Westphal nuclei in the pretectum [12], [13], as illustrated in Figure 1. In order to evaluate the effect of these functions on PLRs, the responses of both eyes were employed in the evaluation, instead of a single eye [14], [15]. The specific metrics for some of the differences of each eye should be introduced in order to evaluate the activity of these functions. Of course, a participant's age is the major factor in the diagnosis of dimentia, and along with features of PLRs is a key piece of information.

This work was partially supported by the Japan Science and Technology Agency (JST) [JPMJTM20CQ, 2020-2022].

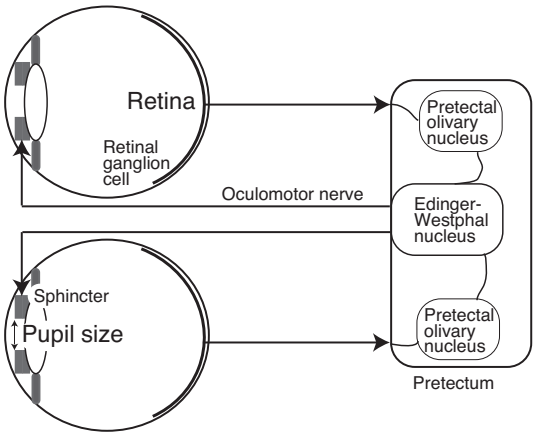


Fig. 1. PLR reaction system based on reference [16]

This paper will focus on the differences of PLR waveform features of both eyes, and their contributions to the level of dementia is evaluated, in addition to experimental factors such as the colour of the light pulses, whether the left or right side eye is irradiated, and the sequences of the light pulses.

The following topics are addressed in this paper.

1) Features of PLRs to blue and red light pulses of the irradiated and non-irradiated eyes are compared, and the differences are evaluated.
2) In order to classify the participants as AD/MCI or normal control group (NC), two types of functions predicting the probabilities of patients are developed using the extracted features of PLRs.

## II. Method

PLRs of dementia (AD or MCI) patients and elderly persons not diagnosed with the disease (NC: Normal Control) were



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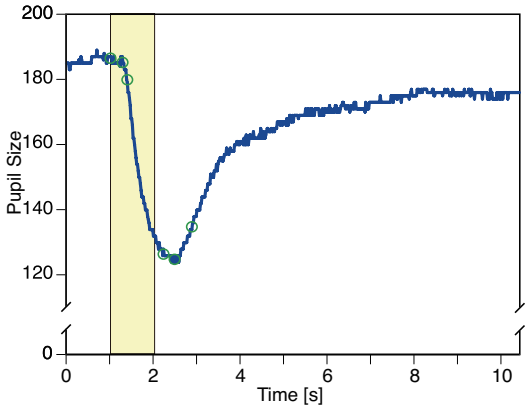


Fig. 2. Example of PLR [14], [15]

measured.

### A. Measuring pupil reactions

Pupil diameters of both eyes were measured for 10 sec. in a temporal darkened space under the following conditions [14].

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 1 second light pulses of blue (469nm, 14.3$cd/m^2$, 6.5lx) or red (625nm, 12.3$cd/m^2$, 10.5lx) light were irradiated on either eye using Condition 2 $\sim$ 5, as producing PLR waveforms as shown in the example in Figure 2. The waveform diameters were measured in pixels using a piece of specialized measuring equipment (URATANI, HITOMIRU).

### B. Participants

Selected participants were clinically examined using MMSE tests, and all participants were classified into three levels with regard to score, such as AD (Alzheimer's disease, with MMSE<=23), MCI (Mild cognitive impairment, with 23<MMSE<=27) and NC (Normal control, including no MMSE scores). Two sets of measured data were prepared for the 2 different periods.

1) Data set 1: Blue light sessions such as Conditions 1 $\sim$ 5 were assigned first [14], [15].
   - AD: 31 (Mean age:83.0, SD:6.3).
   - MCI: 9 (Mean age:82.1, SD:6.3).
   - NC: 61 (Mean age:75.6, SD:9.2).
2) Data set 2: All participants were measured twice in two sequential sessions which were conducted beginning with Blue light sessions (Conditions 1 $\sim$ 5) or Red light sessions (Conditions: 1,4,5,2,3) in random combinations.
   - AD: 12 (Mean age:80.7, SD:5.5).
   - MCI: 2 (Mean age:83.5, SD:7.8).

The measurement observations were conducted by a clinical physician at two medical institutions, and the procedure was approved by an ethics committee at Osaka Kawasaki Rehabilitation University.

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 |

TABLE II
FACTOR LOADING MATRIX FOR PLR FEATURES [14], [15]

| Variables | Factor1 | Factor2 | Factor3 |
|---|---|---|---|
| diff_min | **0.87** | -0.13 | 0.09 |
| diff2_min | **0.76** | 0.06 | 0.16 |
| diff2_max | **-0.83** | -0.17 | 0.22 |
| diff_max | -0.36 | 0.08 | 0.15 |
| RA | -0.24 | **0.78** | -0.09 |
| t_min | 0.22 | **0.73** | 0.14 |
| t_diff2_min | -0.13 | -0.00 | **0.49** |
| t_diff_min | -0.05 | -0.03 | 0.36 |
| t_diff_max | -0.11 | 0.23 | 0.36 |
| t_diff2_max | 0.06 | 0.07 | 0.30 |

Factor1: differential & acceleration
Factor2: miosis size and minimum time
Factor3: time components

### C. PLR waveforms and feature extraction

Condition 1 was designed to observe the degree of pupillary oscillation while at rest. Subsequently, the frequency powers of both eyes were calculated separately [17]. The frequency powers are summarized for each eye in three frequency bands as PSD1:$\sim$1.6Hz, PSD2:1.6$\sim$4.0Hz, and PSD3: 0.35$\sim$0.7Hz.

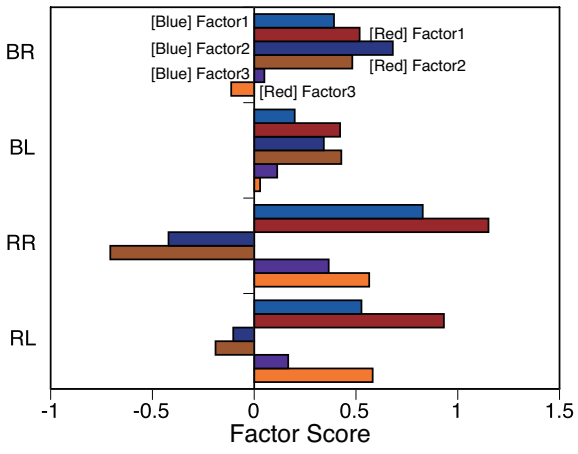


Fig. 3. Comparison of factor scores in Data set 2 in order to extract the order effect of the light pulses (Blue or Red light)

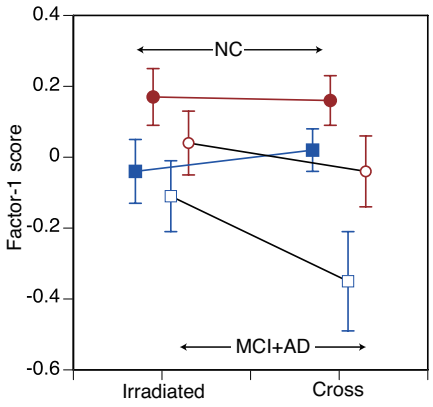


Fig. 4. Data set 1:Factor1(differential & acceleration)

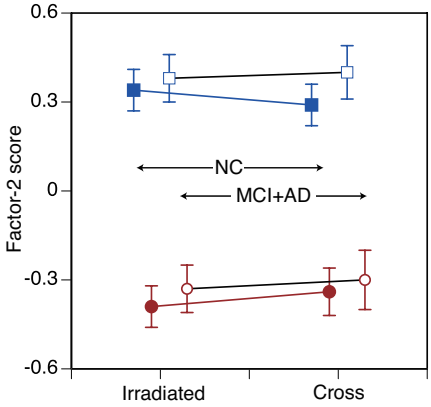


Fig. 5. Data set 1:Factor2(miosis size and the time)

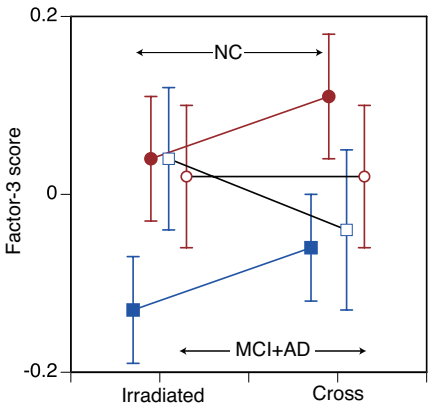


Fig. 6. Data set 1:Factor3(time components)

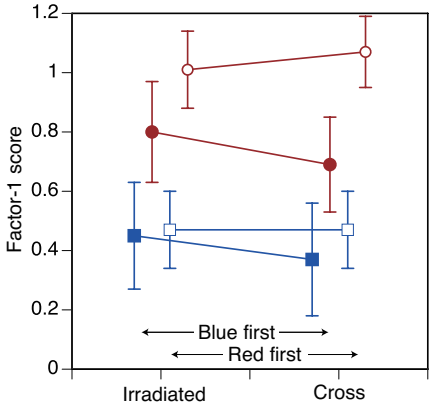


Fig. 7. Data set 2:Factor1(differential & acceleration)

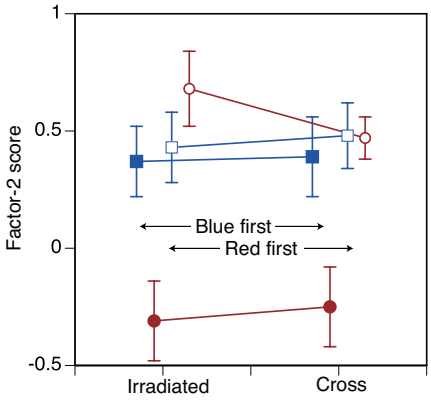


Fig. 8. Data set 2:Factor2(miosis size and the time)

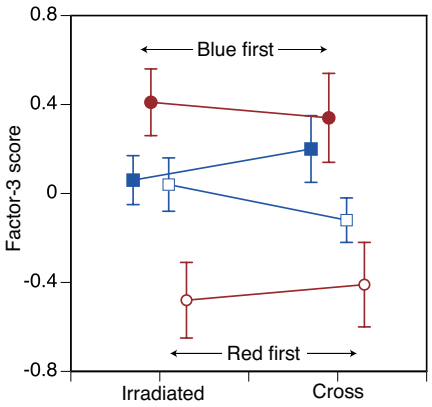


Fig. 9. Data set 2:Factor3(time components)

A typical PLR reaction is illustrated in Figure 2, and several features of waveforms were extracted, as shown in Table I, which shows variable names and their short descriptions [3], [14]. The latent factors were extracted using factor analysis, and the contribution ratio is 45.5%. The factor structure and loading matrix are shown in Table II. Their factor scores are calculated as meta features [3], [14].

## III. Results

### A. Order effect of coloured light pulses

During an analysis of Data set 1, an order effect of light pulse presentation was suspected since some differences were observed between the two coloured light pulse conditions. In order to examine the effect, means of factor scores in two sequences were compared using Data set 2. The means of blue first and red first sessions are summarised in Figure 3. The means of factor scores in the two sequences were compared. The differences between the two sequences were tested statistically, and the differences were not significant ($p > 0.05$). Also, there are no significant difference in factor scores of patients in the two sets of data. Patient's response data in the two data sets is comparable ($p > 0.05$). Therefore, the order of the light pulses (blue or red light first) of the two data sets is not significant. However, as there are some differences in factor scores for each eye, these contributions were analyses as follows.

### B. Differences of factor scores for irradiated and non-irradiated eyes

Factor scores of features of PLRs are compared to reactions of eyes which have been irradiated (Irradiated) or have not been irradiated, such as Cross reaction with the EW nucleus. Factor scores of Data Set 1, which uses blue and red coloured light pulses (blue vs. red) as two conditions with the groups of participants (NC vs. MCI+AD), are summarized and the responses of each eye when irradiated directly or in cross condition are compared. The results are illustrated in Figures 4∼6. Responses to light pulse irradiation of both eyes are summarized using the hypothesis that there are a few differences between the two eyes. For each factor score, the light pulse colour affects the differences. The factor of the light pulse colour is significant for each subject group according to the results of Two-way ANOVA, except for Factor3 in the MCI+AD group. The factor for observed eyes (Irradiated vs. Cross) is significant for Factor1 scores of the MCI+AD

TABLE III
LOGISTIC REGRESSION MODELS FOR MCI AND AD WITH NC GROUPS FOR DATA SET-1

| Model | Variables of extracted features | N of variables | SEL | AUC |
|---|---|---|---|---|
| 2n* | (R)(L)[3factor x 4 cond. + PSD1-3], age | 31 | 31 | 0.95 |
| 2ns* | age,brr1-2,brl3,blr1-3,bll1-3,sPSD3,dPSD3 | 31 | 14 | 0.92 |
| 2a* | the same condition for 2n [AD vs. MCI+NC] | 31 | 31 | 0.95 |
| 2as* | brr1-2,brl3,blr1-3,bll1,bll3,rrr2,rrl2,PSD3 | 31 | 13 | 0.89 |
| 3n | age,(Irradiated & Cross)*3Factors*2Colour,PSD1-3 | 16 | 16 | 0.83 |
| 3ns | age,IbF3,IrF1,XbF1-3,XrF3,PSD1,PSD3 | 16 | 9 | 0.81 |
| 3a | age,(Irradiated & Cross)*3Factors*2Colour,PSD1-3 | 16 | 16 | 0.80 |
| 3as | IbF3,IrF1,XbF2,XrF1,PSD2 | 16 | 5 | 0.77 |
| 4n | age,(Products + Rates)*3Factors*2Colour,PSD1-3 | 16 | 16 | 0.80 |
| 4ns | age,PbF1-2,PSD1,PSD3 | 16 | 5 | 0.77 |
| 4a | age,(Products + Rates)*3Factors*2Colour,PSD1-3 | 16 | 16 | 0.86 |
| 4as | PrF2,DbF3,DrF1,PSD2 | 16 | 4 | 0.77 |
| 5n | age,(Irradiated & Cross + Products + Rates)*3Factors*2Colour,PSD1-3 | 28 | 28 | 0.89 |
| 5ns | age,IbF2-3,IrF1,XbF1-3,XrF1,PrF1,DrF1,ff1-ff3 | 28 | 13 | 0.84 |
| 5a | age,(Irradiated & Cross + Products + Rates)*3Factors*2Colour,PSD1-3 | 28 | 28 | 0.89 |
| 5as | IbF2-3,IrF1,XrF1,PbF1,PrF2,DrF1,DrF3 | 28 | 8 | 0.84 |
| 6nL | age,(Irradiated & Cross + Products + Rates)*3Factors*2Colour,PSD1-3 | 28 | 28 | 0.89 |
| 6nLs | age,IbF1-3,IrF2,XbF2-3,PbF2,PrF2,DbF2,DrF3,PSD1-3 | 28 | 13 | 0.87 |
| 6nR | age,(Irradiated & Cross + Products + Rates)*3Factors*2Colour,PSD1-3 | 28 | 28 | 0.93 |
| 6nRs | age,IbF1-3,XbF3,XrF2,PbF2,DbF2,DrF3,PSD1,PSD3 | 28 | 11 | 0.88 |
| 6aL | age,(Irradiated & Cross + Products + Rates)*3Factors*2Colour,PSD1-3 | 28 | 28 | 0.92 |
| 6aLs | age,IbF2-3,XrF3,PrF2,PSD1 | 28 | 6 | 0.81 |
| 6aR | age,(Irradiated & Cross + Products + Rates)*3Factors*2Colour,PSD1-3 | 28 | 28 | 0.97 |
| 6aRs | age,IbF3,IrF3,XbF2-3,XrF1-2,PbF1,PrF1-3,DbF1,DrF3,PSD2 | 28 | 14 | 0.93 |

SEL: the number of selected variables; *: reported in our previous work [15]

group ($F(1, 40) = 5.64$). This means that there are significant differences in Factor1 scores for velocity and acceleration of PLRs between the two eyes. In addition, there are some differences in Cross Factor1 and Irradiated Factor3 scores for blue light pulses, while there are few differences in Factor2 scores. There are few differences in factor scores for red light pulse except for Cross-Factor3 as well.

These behavioural characteristics are confirmed in considering two types of light pulse sequences using another data Set, Data Set 2. The results are summarized in Figures 7∼9 using an identical format as in Figure 4∼6. In Data Set 2, two kinds of plots represent two light sequences since all participants are patients. In comparing the means of the two sequences, those for blue light pulses are almost similar, but there are some differences in means for red light pulses. The responses to red light pulses seem unstable. Also, the factor of the light pulse colour was significant for factor scores of the first sequence of red light pulses. The effect of irradiated eyes (Irradiated or Cross) on means of factor scores is significant for Factor1 scores of the first blue sequence, and Factor2 scores of the first red sequence. The results of Factor1 coincide with the results of Data Set 1 in Figure 4.

### *C. Relationship between responses of irradiated and non-irradiated eyes*

Previous results suggest that the deviations in the factor scores for two eyes, when directly or cross irradiated, are relatively smaller than the deviations in factor scores with other conditions. In order to evaluate the relationships between the responses of the two eyes, some new metrics are introduced in order to classify patients and NC participants. In regards

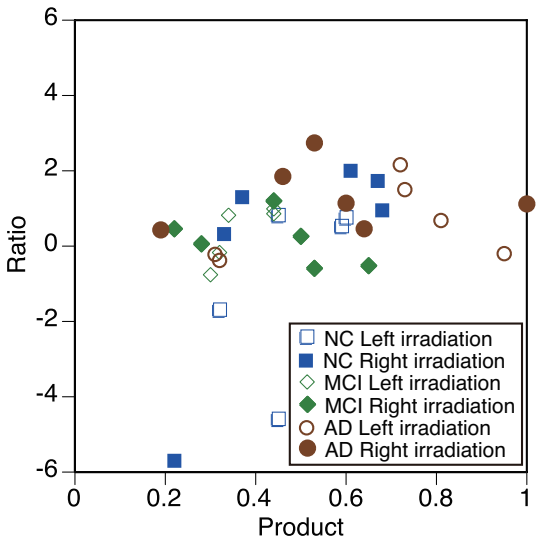


Fig. 10. Product and ratio of factor scores between irradiated and non-irradiated eyes.

to previous studies, the relationship may represent a disorder related to PLR reactions. Here, one pair of original metrics is introduced as a result of trial and error evaluations. The pair may represent asynchronous response characteristics as a dissimilarity between the responses of the two eyes.

$$Product_{\{b|r,F_j\}} = iFactor_{b|r}j \times xFactor_{b|r}j, (j = 1, ., 3)$$

$$Rate_{\{b|r,F_j\}} = \frac{iFactor_{b|r}j}{xFactor_{b|r}j}, (j = 1, ., 3)$$

In the equations, $iFactor_{b|r}j$ means $j$th ($j = 1, 2, 3$), for factor scores of eyes irradiated using blue or red light pulses. $xFactor_{b|r}j$ means $j$th factor scores on blue or red non-irradiated (cross reaction) eye.

These metrics are summarized in Figure 10. The horizontal axis represents the product value, and the vertical axis represents the rate value. Pairs of products and rates are calculated from 3 sets of factor scores for two colours of light pulses on either eye (2×2). They are summarized for the three levels of participants, where plots for left irradiation are illustrated as symbols with no fill and plots for right irradiation are illustrated as solid symbols. All plots deviate along both product and rate axes. Most of the AD patients show higher values for the products, and some of MCI patients show lower values for the products. Some of the NC participants deviate along the rate axis. In comparing the three scatter grams, the distributions of the two-dimensional values for the the three levels of participants are slightly different. In particular, the mean of the products for AD patients (0.61) is higher than the mean for MCI patients (0.40), and the mean for NC participants (0.48) is the middle of the two groups of patients. Though the differences are small, these positive contributions to the classification of patients will be confirmed in the next section of the paper.

### *D. Classification of dementia levels of patients*

In order to classify participants into three levels of dementia, two logistic regression functions were introduced using the extracted factor scores of both eyes. Also, power spectrum densities of pupil oscillation (PSD1 ∼ PSD3) are introduced. The two regression functions consist of classifying NC or MCI+AD participants and NC+MCI or AD patients in Data Set 1 [15]. The logistic regression function provides the probability of each classification, such as whether NC or patient. Since both regression functions are used for binary classification, prediction performance is evaluated using AUC (Area Under the Curve) of a ROC (Receiver Operation Characteristics) curve. The AUC for extracting AD patients is sometimes unstable, as the number of AD patients is limited. The performance of the previous regression models is summarized at the top of Table III. Performance is based on Data Set 1. The model "2n" is used for classifying NC or MCI+AD patients, and model "2a" is used for extracting AD patients from NC+MCI participants. The factor scores of the four conditions 2 to 5 are employed in these functions. In assessing the contribution of factor scores, selection of variables using a step-wise procedure is employed to calculate the function values for models "2ns" and "2as". Most AUCs for validation of the performance of Data Set 1 are over 0.9. Prediction performance of patient detection rates for Data Set 2 are around 50% when the threshold for probability is set to 0.5 on models "2n" and "2a". Performance is different for the two sequences of colour light pulses.

In the previous section, factor scores for the left and right eyes are summarized into the scores for irradiated or non-irradiated (cross) eyes. The number of variables for both eyes can be reduced by half, because the factor scores for irradiations of the left and right eyes using each colour of light pulse have been averaged. When these factor scores are applied to two types of regression functions for models "3n" and "3a", the performance AUCs show lower performance values than those for models "2n" and "2a". Another set of metrics to measure product ($Product\_b|r, F_j$) and rate ($Rate\_b|r, F_j$) of factor scores of irradiated and non-irradiated (cross) eyes are also employed for the two regression functions. However, detection performance is lower than the performance in the previous study.

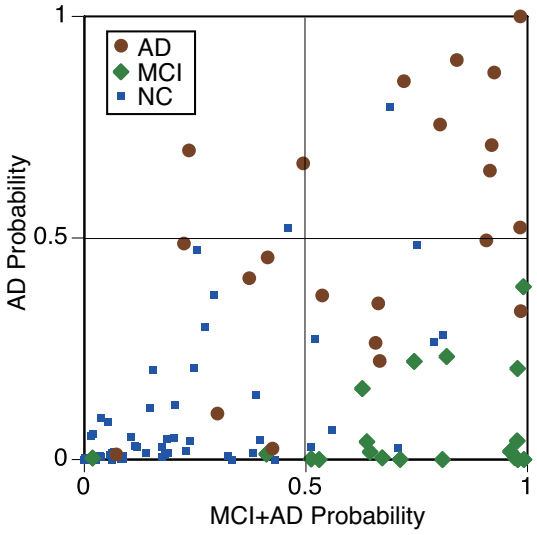


Fig. 11. Probabilities of trained data for irradiated left eyes using models "6nL" and "6aL".

In the next step, two types of metrics are introduced simultaneously using combinations of models "3n" and "4n" or "3a" and "4a". The performance of model "5" improved in comparison with models "3" and "4". Here, three sets of models employ mean factor scores of left and right eye light pulses. Most variables are based on the responses to light irradiated or non-irradiated eyes. Therefore, these variables can be transformed into two sets for irradiated left or right eyes. The extracted metrics may represent features of the reaction mechanism for both eyes, since the metrics are generated from reactions of both eyes. In the section for model "6", AUCs of the sets of data for both the left and right eyes are summarized independently. The performance of model "6" is comparable with values for model "5". As the data is divided into sets for right and left irradiated eyes, and both sets provide similar performance, estimation may be possible using two colour light pulses instead of four conditions.

Classification results for Data Set 1 using models "6nL" (NC detect) and "6aL" (AD detect) are summarized in Figure 11, where the horizontal axis represents the probability of MCI+AD and the vertical axis represents the probability of AD. The two-dimensional region is divided into four sub-regions by two thresholds of probability of 0.5 each. Most NC participants are classified into the low probability sub-regions,

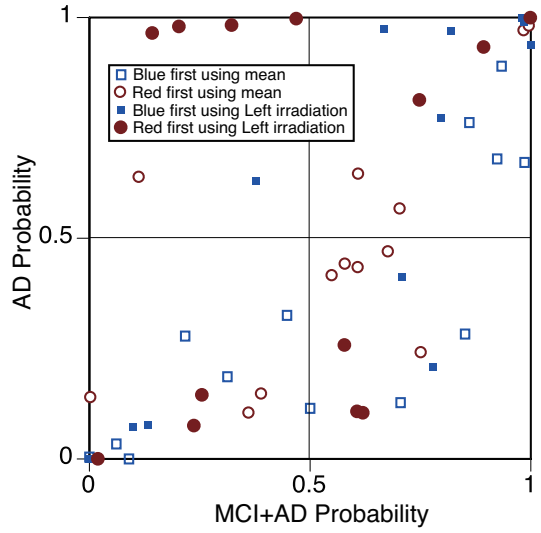


Fig. 12. Two sets of prediction result using two models: Mean features and features of irradiated left eyes using two sets of models, with symbols with no fill for models "5n" and "5a", and solid symbols for models "6nL" and "6aL".

as shown in Figure 11. Some AD patients are classified into the bottom-right sub-region, such as those with MCI, but most MCI patients are classified into the appropriate sub-region.

In order to validate the performance of the models, extracted features of two sequences in Data Set 2 are applied to the models, and the predictions are compared. As mentioned above, 54% of patients are detected using a probability threshold of 0.5 for the first blue sequence, and 38% of ADs are detected using the first red sequence when model "2n" is introduced.

The updated results for Data Set 2 are summarized in Figure 12 using model sets "5" and "6". In Figure 12, the symbols with no fill are the predicted probabilities using models "5n" and "5a", and the solid symbols are the predicted probabilities using models "6nL" and "6aL". When models "5n" and "5a" are employed, 54% of patients are detected using the first blue light sequence, and 77% of patients are detected using the first red sequence. In addition, 77% of patients are detected during both sequences when models "6nL" and "6aL" are introduced. These results suggest the possibility of reducing measurement trials to one light pulse to either eye using two colours, and improving prediction performance of other data sets.

The robustness of this procedure should be examined using other data sets which consist of patients and NC participants of various ages. In this study, the classification of participants was based on only MMSE scores as mentioned in the section about participants. Since there are many indices of dementia, additional information should be considered in order to diagnose the symptoms of the disease, including participants' personal histories. The confirmation of the contribution of these additional procedures to the diagnosis of dementia will be a subject of our further study.

## IV. Summary

In order to detect persons who may have symptoms of dementia, additional features of PLRs are defined and applied to classify the level of dementia using two types of logistic functions. Prediction performance was evaluated using two sets of surveyed data obtained from clinical institutes. In particular, the following points were discussed.

1) PLR observation procedures were evaluated using two sequences of combinations of light pulses. In the results, the order of the colour of the light irradiation was not significant for the extracted factor scores.
2) Two metrics were introduced to represent the characteristics of irradiated and non-irradiated eye reactions of PLRs. Since these metrics can be generated when either eye is irradiated by chromatic light, another type of classification procedure was performed using the features of PLRs and the two functions.
3) Prediction performance of patients with dementia is evaluated using several conditions which are based on two types of functions for identifying two levels of patients such as those with MCI or AD. These models are trained using Data Set 1, and their performance was validated using Data Set 2.

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

## Acknowledgement

The authors would like to thank Prof. Masatoshi Takeda and Prof. Takenori Komatsu of Osaka Kawasaki Rehabilitation University, Toshinobu Takeda, MD at the Jinmeikai Clinic, Yasuhiro Ohta and Takato Uratani of the Uratani Lab Company Ltd. for their kind contributions.

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