Prediction of Alzheimer's Disease in Patients using Features of Pupil Light Reflex to Chromatic Stimuli

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Abstract—A diagnostic procedure to predict the probability of diagnosing a patient with Alzheimer's Disease (AD) was developed using features of pupil light reflex (PLR) waveforms. 15 features of PLRs for three colours of light pulses at two levels of brightness were measured. Participants were 12 AD patients and 7 control group subjects. A logistic regression analysis was introduced to identify AD patients using two factor scores of features of PLR. The prediction performance of combinations of factor scores for features of PLRs were then evaluated using a test of fitness. An MCMC technique was introduced to estimate the parameters of the regression functions. The model provides a distribution of the probability of diagnosis of AD patients and control group subjects.

I. Introduction

The pupil light reflex (PLR), which produces changes in pupil diameter in response to a light pulse of white or red, has been introduced to diagnose Alzheimer's Disease (AD) [1], [2]. In addition to this, the recent discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs) [3] reveals the possibility of using various diagnostic procedures that involve a shorter light wavelength, such as blue light [4]. For example, PLRs related to ipRGCs can be used to detect symptoms of Age-Related Macular Degeneration (AMD) [5]. Some critical studies have suggested that common sources may be the origin of both AD and AMD diseases [6], [7], [8], [9]. Also, because most AD patients are elderly, the influence of aging on PLRs should be evaluated carefully.

The authors have been studying a diagnostic procedure for detecting AD symptoms using PLRs of various types of light pulses and observing the conditions the light pulses produce [10]. Though these results show the possibility of aiding the diagnosis of the disease, a more flexible procedure is required. In particular, the number of AD patients used in the experimental survey was restricted, and the assessment of the prediction of accuracy was insufficient. Therefore, significant features of PLRs, which can be used in the diagnostic procedure, should be extracted as necessary. If the distribution of features can be estimated, the possibility of diagnosing AD patients may be predicted using the Bayesian process.

In this paper, features of PLRs are extracted and the differences between AD patients and control group subjects

are discussed. Some procedures for predicting the probability of diagnosing AD patients are compared. The following topics are addressed:

1) Features of PLRs are analysed and their factors are extracted. The differences in features and factor scores between AD patients and control group subjects are compared. Also, the influence of aging is evaluated.
2) Logistic regression is introduced to calculate the probability of diagnosing the disease in AD patients and control group subjects. The models of fitness of the groups are then compared.
3) The MCMC technique is introduced to estimate the parameters of the models, and the performance of the models is discussed.

II. Method

A. Participants

A conventional PLR experiment was performed on 19 participants (42~89 years old, mean age:70.6), 12 of which were healthy individuals with normal vision (Control group: 62~89 years old, mean age:72.1) and 7 of which were patients with Alzheimer's Disease (AD Patients: 42~84 years old, mean age:68.1) who had already been diagnosed by medical doctors. It was not easy to invite volunteers who were aged over 80. The age levels are summarised in Table I.

Informed consent was obtained from all participants prior to the experiment.

B. PLR measurement

The stimuli consisted of three chromatic lights, red (635nm), blue (470nm) and white (CIE x:0.28, y:0.31), at two levels of

TABLE I
NUMBER OF SUBJECTS BY AGE

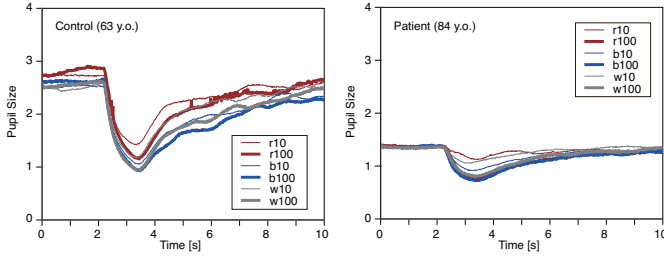| Label	Age	Control	Patient
L	≤ 70	5	3
M	71~80	5	3
H	81≤	2	1

Fig. 1. An example of PLRs for a control group subject and an AD patient
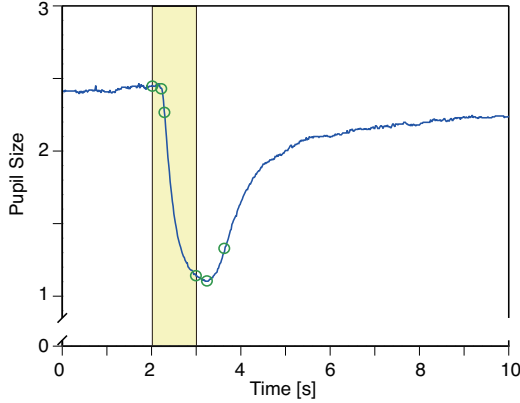
Fig. 2. Feature extraction from PLR responses

TABLE II
DEFINITIONS OF PLR FEATURES

Variable	Definition & notes
ps_base	Mean of the pupil size for time before light pulse
ps_lon	Pupil size where light pulse on
ps_loff	Pupil size where light pulse off
ps_min	Minimum pupil size
RA	Range of pupil size (ps_lon - ps_min)
v_con	Max amplitude of pupil construction velocity
v_rest	Max amplitude of pupil re-constriction velocity
ac_max	Min amplitude of pupil acceleration
t_delay	Pupil response delay
t_min	Time when "ps_min" appears
t_v_con	Time when "v_con" appears
t_v_rest	Time when "v_rest" appears
int_con	Integration of constriction phase
int_rest	Integration of restoration phase
int	Overall integration (int_con + int_rest)

brightness (10 and 100 cd/m^2). These stimuli were labelled as r10, r100, b10, b100, w10 and w100.

The duration of observations was 10 seconds, with the first 2s being a pre-stimulus phase as a rest period, followed by a 1s light pulse and 7s as a restoration phase. Pupil diameters were measured in mm at 60Hz using a system developed by some of the authors [11]. PLRs for each stimuli were observed in single trials using a repeated-measure design.

Examples of measurements for a healthy individual and for an AD patient are shown in Figure 1. In these figures, PLRs are illustrated in response to 6 stimuli, namely the 3 colours and two levels of brightness.

III. RESULTS

1) Feature definitions: A typical PLR waveform shape is illustrated in Figure 2. In the figure, the light pulse overlaps for a period of 2∼3 seconds. As the figure illustrates, there are pupillary response delays due to the shrinking of pupil and its restoration to normal size.

Some features are extracted to specify the PLR response, and these variable features are summarised in Table II. They are pupil size, velocity of pupillary change, duration of change, and integration of the waveform. These features are calculated for each PLR response.

A. Comparison of features

The extracted features for each stimulus were compared between two groups. The results are summarised in Table III.

When there is a significant difference between pairs of values, the values are displayed in bold face. As the table shows, there are many significant pairs for the b100 and r10 conditions, but few pairs for the white stimulus. In regards to the significant differences for the b100 condition, such as pupil size, velocity and acceleration of pupillary change, the pupil size for AD patients is relatively small, and responds slowly.

All participants are elderly, and in addition to being AD patients, their ages may affect pupil responses. Therefore, the effect of two factors (participant group and age level) on pupillary changes is examined using two-way ANOVA. The variables with deviations which contribute most significantly are selected and summarised in Table IV using means across age levels. These means change along with age levels. Most variables selected are related to velocity and time delay. Since there are few significant interactions between the two factors, they may be independent of each other in regards to PLR features. Additionally, most significant differences between age levels appeared for white stimulus and most differences between two groups occurred when w100 light was used. These results may be related to the mechanism of the PLR, and thus a detailed analysis of this will be a topic of our further study.

B. Factor analysis

There are significant differences in some of the PLR features of the AD and control groups. Though their variables exhibit the qualitative tendencies of a change, their sources could not be determined, as the physical variables and measurement units are completely different; some are expressed using sizes and others are expressed as velocities or accelerations.

Factor analysis was used to extract latent sources of the variables which were measured repeatedly. Since overall integration (int) is a summation of two parts such as int_con and int_rest, it has been omitted during the analysis, thus 14 variables were measured. A two factor structure was estimated using a principal component solution and a screw plot. A factor loading matrix using Promax rotation was produced, as shown in Table V.

TABLE III
MEANS OF PLR FEATURES

Feature Variable	b10(N=19)		b100(N=17)		r10(N=18)		r100(N=19)		w10(N=19)		w100(N=19)	
	Control	Patient	Control	Patient	Control	Patient	Control	Patient	Control	Patient	Control	Patient
ps_base	19.88	16.69	**20.51**	**14.21**	**20.16**	**14.37**	19.59	16.41	19.2	16.40	19.20	16.46
ps_lon	20.24	16.72	**20.81**	**14.18**	**20.29**	**14.22**	20.00	16.26	19.56	16.54	19.45	16.46
ps_loff	10.90	8.02	**9.76**	**6.76**	13.02	9.29	10.15	7.68	11.61	8.80	9.14	7.03
ps_min	10.68	7.59	**9.20**	**5.88**	12.75	8.96	9.76	7.21	11.31	8.56	8.77	6.29
RA	9.56	9.13	**11.60**	**8.30**	7.53	5.27	10.24	9.05	8.26	8.08	10.69	10.17
v_con	-0.46	-0.47	**-0.51**	**-0.31**	**-0.36**	**-0.22**	-0.44	-0.37	-0.40	-0.40	-0.48	-0.42
v_rest	0.13	0.10	**0.18**	**0.08**	**0.13**	**0.08**	0.16	0.10	0.14	0.10	0.14	0.11
ac_max	-0.06	-0.07	**-0.07**	**-0.04**	**-0.05**	**-0.03**	-0.06	-0.05	-0.06	-0.05	-0.07	-0.06
t_delay	0.24	0.26	0.23	0.24	0.25	0.26	0.24	0.25	0.26	0.28	0.23	0.23
t_min	**1.13**	**1.31**	**1.30**	**1.43**	1.09	1.26	1.22	1.36	1.10	1.22	**1.26**	**1.41**
t_v_con	0.34	0.35	**0.33**	**0.36**	0.35	0.39	0.37	0.37	0.37	0.38	0.32	0.33
t_v_rest	1.84	1.78	1.91	2.14	1.65	2.06	1.88	2.11	1.67	1.96	1.74	1.98
int_con	293.1	277.0	**345.0**	**211.0**	**230.0**	**144.5**	301.5	260	249.4	241.6	330.5	300.3
int_rest	748.5	823.0	1015.9	802.7	532.1	444.1	849.8	796.9	612.6	652.3	906.9	941.7
int	1041.6	1100	1361	1014	762.1	588.7	1151.3	1056.9	862.0	893.9	1237.3	1242.0

pairs of **bold means** show significant differences

TABLE IV
AGE AFFECTED FEATURES (LIST OF SIGNIFICANT VARIABLES)

		age levels		
Stimulus	Variable	L	M	H
b10	ac_max	-.11	-.05	-.04
b100	ps_min	8.0	6.9	10.9
r10	t_v_con	0.37	0.36	0.43
r100	t_delay	0.23	0.24	0.31
	int_con	381.4	249.5	176.3
w10	RA	11.2	7.9	4.7
	v_con	-.64	-.33	-.25
	ac_max	-.09	-.04	-.03
w100	RA	14.3	9.6	7.6
	v_con	-.64	-.39	-.33
	t_v_con	0.28	0.34	0.36
	int_con	459.6	280.8	217.9
	int_rest	1279.1	853.7	659.8
	int	1738.8	1134.5	877.7

Age factor is significant ($p < 0.05$)

TABLE V
FACTOR LOADING MATRIX FOR PLR FEATURES WITH PROMAX ROTATION

Variables	Factor1	Factor2
ps_base	**0.596**	**0.586**
ps_lon	**0.596**	**0.586**
int_rest	**1.007**	-0.271
RA	**0.997**	-0.064
int_con	**0.988**	0.006
v_con	**-0.906**	-0.067
ac_max	**-0.902**	-0.021
t_v_con	**-0.737**	0.110
t_delay	**-0.712**	0.062
v_rest	**0.643**	0.099
ps_min	-0.111	**1.025**
ps_loff	-0.079	**0.999**
t_min	0.086	**-0.643**
t_v_rest	0.066	**-0.438**
Contribution ratio(1)	0.42	0.21
Contribution ratio(2)	0.52	0.32
Correlation between factors		r=0.38

(1): Each factor with other factors eliminated
(2): Each factor with other factors ignored

The fundamental variables of each participant, such as pupil sizes commonly contribute to both factors. The second factor contains variables which are concerned with features of the progress of restoration of the pupil after a pulse of light, and the first factor contains the remaining variables of the features of PLR. As mentioned above, both factors contain two variables, and there is a significant correlation between these two factors ($r = 0.38$). Since even the contribution ratio of each factor when the other factors are eliminated is over 60%, the two factors can account for the deviation.

The factor scores ($factor1, factor2$) were calculated using the factor loading matrix, and their means for each stimuli are summarised in Figure 3 according to group. The horizontal axis indicates the first factor, and the vertical axis indicates the second factor. The error bars show standard errors. The two groups are indicated using suffixes, such as "p" for patients, or "c" for the control group.

When means between the two groups are compared for red (r10 and r100) or white (w10 and w100) stimulus lights, they are located in proximity to each other, but the means of the two groups are relatively far apart from each other for blue stimulus lights (b10 and b100). Pupil reactions in response to light colours are represented in Figure 3. In the results of applying t-tests to pairs of the means for the two subject groups, there are significant differences in the first factor scores for b100 ($t(15) = 2.64$, $p < 0.05$), in the second factor scores for b100($t(15) = 2.88$, $p < 0.05$) and for w100($t(17) = 2.15$, $p < 0.05$). Also, differences without much significance were observed for the second factor scores for b10($t(17) = 2.07$, $p < 0.10$) and for r10($t(17) = 1.77$, $p < 0.10$).

The results show that between the two subject groups there are significant differences in both factor scores for the b100 condition. As Table III shows many significant differences, the factor scores also represent these differences. Also, the second factor seems to reflect the difference in features of PLR between the two groups.
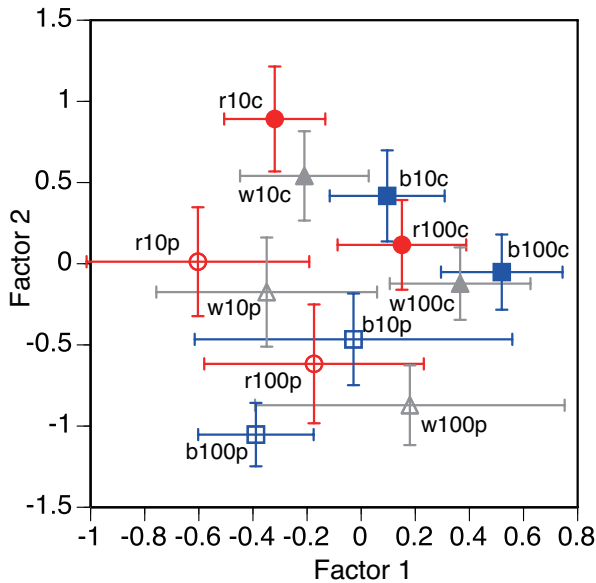
Fig. 3. Distributions of factor scores with error bars showing standard errors

TABLE VI
PERFORMANCE OF MODELS

Stimulus	AIC	R^2	Accuracy	AUC
b10	25.16	0.26	82.1	0.82
b100	17.24	0.47	89.4	0.89
r10	27.33	0.17	73.8	0.74
r100	28.05	0.14	72.6	0.73
w10	27.35	0.18	69.0	0.69
w100	24.70	0.28	79.8	0.80
b(10+100)	21.07	0.48	89.4	0.89
r(10+100)	30.26	0.22	71.4	0.71
w(10+100)	22.94	0.47	90.5	0.91
b+r	18.50	0.73	100	1.00
r+w	29.70	0.50	95.2	0.95
b+w	18.00	0.73	100	1.00
b+r+w	26.00	0.73	100	1.00

Though the influence of age level on factor scores was analysed, it did not affect either factor.

C. Introducing logistic regression

As mentioned in the introduction, this paper introduces logistic regression analysis to estimate the probability of diagnosing AD patients using a binary response variable (p) and PLR features. Here, $p = 1$ for the control subject and $p = 0$ for the AD patient, then p is given by the following equation with logit function.

$$\hat{y}_i = a + b_1 factor1_{i,j} + b_2 factor2_{i,j}$$
$$p_i = \text{logit}^{-1}(\hat{y}_i) = \frac{1}{1 + \exp(-\hat{y}_i)}$$

Suffix i represents the subject, and suffix j represents the stimulus light condition.

Logistic regression analysis was applied to the above factor scores for several conditions, such as the two factor scores for a specific stimulus light condition (light intensity: 10 or 100),
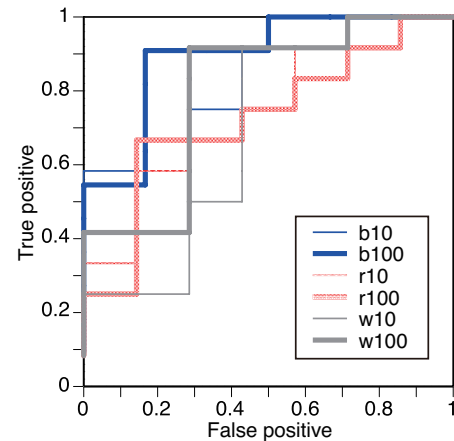

Fig. 4. Comparison of ROC curves

four factor scores for a colour condition (blue, red and white including light intensity 10 and 100) and further combinations such as two colours or all conditions (6 conditions and 2 factor scores). Every model was evaluated for fitness of model using AIC (Akaike Information Criteria), and prediction accuracy using R^2. The accuracy was measured using an appropriate threshold, and performance was summarised using two dimensional metrics such as true positive and false positive. The relationships are then illustrated as ROC (Receiver Operating Characteristics) curves. Figure 4 shows ROC curves of every stimulus condition. The surface area of the curve is also a measure of the AUC (the area under the ROC curve). Their indices are summarised in Table VI.

Results of analyses suggest that discriminant performance is higher for blue light stimuli, in particular for the b100 condition. The ROC curves show step-wise changes, since the number of participants influenced the results. However, the performance of AUC for b100 produced the highest reaction of any single stimulus condition.

D. Model parameter estimation

As Table III shows the possibility of discriminating between AD patients and control group subjects using a logistic regression function. However, the parameters of these functions can not be estimated sufficiently because the amount of data is too limited. Here, the Markov chain Monte Carlo (MCMC) method was introduced for more accurate estimation of the parameters. In regards to the data generation procedure using the MCMC technique, the burn-in period was 2000 and the number of samples was 10000 [12]. Using this procedure for the b100 condition, the parameters are estimated as follows.

$$\hat{y}_i = 5.4229 + 0.4722 * factor1_i + 7.3801 * factor2_i$$

The magnitude of coefficient for the second factor ($factor2$) is 15 times that of the coefficient for the first factor ($factor1$).

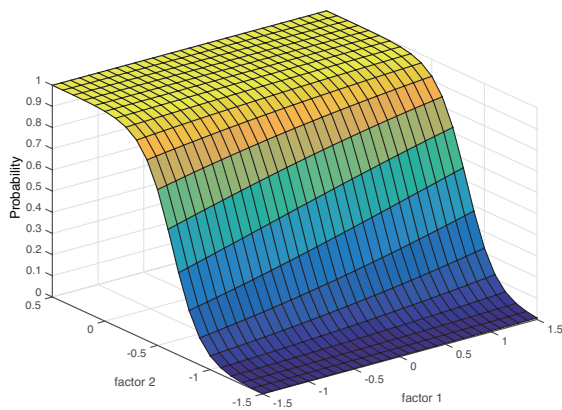As an additional example, the parameters for blue light stimuli were estimated as follows:

Fig. 5. Probability distribution for b100

$$\hat{y}_i = 9.1664 + 2.5320 * factor1_{i,b10} - 1.1366 * factor2_{i,b10}$$
$$-1.4011 * factor1_{i,b100} + 12.0891 * factor2_{i,b100}$$

The magnitude of these parameters suggests that the coefficient for the second factor at a high level of brightness (b100) is relatively larger than for others (b10 and the first factor at a low level of brightness). As the patterns of coefficients depend on the light stimulus, the wavelengths of the stimuli may affect these reactions.

In regards to the discussion in the previous section, the probability of control group subjects (1) or AD patients (0) may be illustrated using two dimensional information ($factor1$ and $factor2$), as shown in Figure 5. Figure 5 shows that the probability distribution against patients with AD depends mainly on the scores of the second factor. Also, the score of the first factor helps to more finely adjust the probability during the period where the curve is steep.

In regards to the experimental procedure, the features of PLR can be measured best during a one second high brightness level pulse of blue light (b100). Also, factor scores were calculated using the factor loading matrix shown in Table V. Finally, the probability of diagnosing AD patients can be predicted using the function above.

However, the possibility of developing a more flexible procedure for use in future experiments involving additional new participants will be a subject of our further study.

IV. Summary

This paper presents a procedure for predicting the probability of diagnosing AD patients using features of PLR, which respond to the activities of ipRGCs.

Three colour lights at two levels of brightness were illuminated for 1 second, and pupil light responses were observed. 15 features were extracted from each PLR, and two factor scores were calculated using a factor loading matrix. The following results were produced.

1) There are significant differences in some features between AD patients and control group subjects, in particular for the b100 condition. Also, for a few features for white light there are significant differences between age levels.
2) Logistic regression analysis was introduced to discriminate AD patients from the control group using two factor scores in response to chromatic stimuli. The performance was evaluated using the indices of the fitness of equations. As a result, the performance for b100 was the highest.
3) The MCMC technique was introduced to estimate the parameters of the regression functions. The model provides a distribution of probability for AD patients and the control group.

The validity of the probability estimations should be confirmed using the PLR data of patients. This will be a subject of our further study.

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