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Detecting Alzheimer's Patients using Features in Differential Waveforms of Pupil Light Reflex to Chromatic Stimuli

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Abstract

A procedure to detect irregular signal responses to the pupil light reflex (PLR) was developed in order to detect Alzheimer's Disease (AD) using a functional data analysis (FDA) technique and classification with an Elastic Net. In considering the differences in features of PLRs between AD and normal control (NC) participants, signals of summations and differentials between experimental conditions were analysed. The coefficient vectors for B-spline basis functions were introduced, and the number of basis functions was controlled to produce an optimised model. Model trained data was created using a data extension technique in order to enhance the number of participant observations. In the results, the required number of basis functions for differential signals is larger than the number for the their summation signals, and the features of differential signals contribute to classification performance.

Keywords: Pupil Light Reflex, Alzheimer's Disease, Functional data analysis

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1. Introduction

1.1. Waveform analysis of the Pupil Light Reflex

Irregular signal detection is often applied to diagnostic procedures. Though the simple pupil reaction to a flash of light is well known as the pupil light reflex (PLR), the responses are influenced by conditions of retinal ganglion cells and optic nerves such as Edinger-Westphal Nucleus [1]. In order to distinguish people pseudo positive with Aged-macular degeneration (AMD) or Alzheimer's disease (AD) from a normal control group (NC), differential signals of pupil responses under several observation conditions are examined [2–5]. In particular, pupil responses based on intrinsically photosensitive retinal ganglion cells (ipRGCs) [6] are often compared in order to detect irregular responses and used as diagnostic procedures with patients [7, 8]. Since PLR observation can be conducted in-person using a general-purpose device with a head-mounted display (HMD), the response data can be accumulated during people's daily lives. If specific features of PLR waveforms can be detected effectively using these observations, it may be possible to introduce an early detection procedure for Alzheimer's disease.

1.2. Problems of feature extraction from waveform shapes

The extraction of specific features may be the key to diagnosing patients. Though several trials have been conducted, as mentioned in previous works [2, 9], a more effective procedure should be considered. In particular, localised features in response to characteristics of PLRs to chromatic light. Toward this aim, polynomial spline bases using a B-spline technique effectively extracts local features of the functional data within the time series observations [10]. If some typical features of AD patients could be characterised from waveform shapes, an additional

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Table 1. Comparing feature extraction from waveform shapes

Method	basis function	benefit/limitation
Fourier Descriptor [11, 12]	Fourier basis	Periodic data analysis during observed duration, particularly useful for periodic data [3, 10].
Feature definition	n/a	Some specific features need to be defined in advance such as [13]. Shape similarity is implicitly required for the observation.
Polynomial spline bases [10, 14, 15]	B spline basis	Capturing local features of the functional data which contains local changes.

analytical procedure may be possible. As the features of AD patients show irregular responses, differences between AD and NC groups can be evaluated along with temporal changes in PLR waveforms. These analyses may provide new approaches to the diagnostic procedure.

1.3. Purpose of this paper

In this paper, the contribution of differential signals of PLRs to the experimental process of detecting AD patients using a polynomial spline bases using B-spline technique as a method of functional data analysis, and its effectiveness on the performance of the diagnostic procedure are examined using trained discriminant analysis. The following topics are addressed:

1. The feature extraction procedure for differential signals between responses to chromatic stimuli or levels of light intensity is examined using a functional data analysis technique.

2. Classification performance for AD patients is evaluated using the summation and differential signals of PLRs and their features.

The reminder of the paper is structured as follows. Section 2 reviews previous and related works. Section 3 introduces methodologies for feature extraction from PLR waveforms using functional data analysis and discriminant analysis. Results of performance using discriminant analysis and a comparison of the contributions of factors are discussed in Section 4. The overall summary is presented in Section 5.

2. Related works

2.1. Feature extraction from waveforms

Major approaches are summarised in Table 1. Conventional feature extraction of signal waveform uses Discrete Fourier Transform (DFT), which consists of periodical functions. Features of waveforms or line drawn objects can be noted as Fourier Descriptors [11, 12] using DFT. Though a function-based approach can suppress some of the noise of observations, this technique is constructed using periodical signals without the capture of local features.

In order to emphasise local features, sampling specific feature points presents behavioural characteristics explicitly, as shown in line 2 of Table 1. This approach may focus on specific characteristics in waveform shapes. A feature points-based approach to detecting AD patients shows better performance than using features of Fourier descriptors, but performance remains at a limited level even when an Elastic-Net with Lasso technique is used [16], since local features without focused points may not be considered to be effective [5, 13].

An additional approach may be the use of functional data analysis by introducing polynomial spline bases such as B-spline basis, as shown at the bottom of Table 1. This method can be applied to waveforms flexibly and it may be possible to detect feature contributions during temporal changes using regression analysis, though some tuning of the parameters would be required, however. The differences in performance of biological time series data between two bases functions such as Fourier and B-spline have been examined [10]. In considering the benefit of employing polynomial spline bases, the possibility of diagnosing AD patients using PLR waveforms and this technique is examined.

In this paper, functional data analysis using B-spline basis is simply referred to as functional data analysis (FDA) when later described.

2.2. Diagnosis using PLR waveforms

PLR waveform shapes are influenced by stimulus characteristics of light pulses, such as wavelength (light colour) and intensity (luminance), since the activation of irradiated ganglion cells in response to light stimuli is different. Also, the distributions on the retina and the activated light wavelengths between ganglion cells, cones, rods and ipRGCs are different [2, 6]. As temporal changes in waveform shapes on ganglion cells are also different [9], the possibility for a diagnostic procedure using PLRs for chromatic light pulses has been suggested [4, 7, 8]. Also, PLR waveforms are influenced by ageing and problems with signal transfer pathways from the retina [1]. Therefore, if differential signals between PLR waveforms could be analysed, these differential waveforms may contain

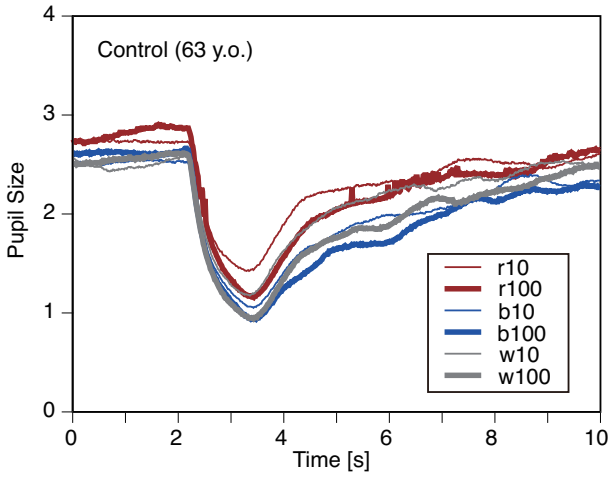

Figure 1. An example of PLRs for a normal control subject

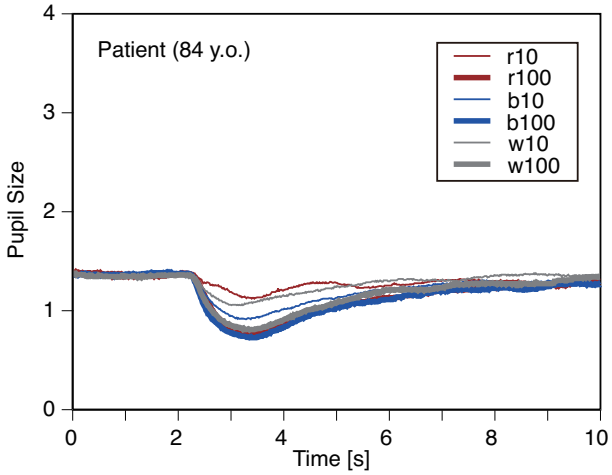

Figure 2. An example of PLRs for an AD patient

specific features about a patient or features of their reaction mechanisms.

In order to create a discriminant function for AD patients, a sufficient number of PLR observations using both patients and a normal control group are required as a reference. With most clinical approaches, possible observation opportunities are limited and individual differences are not small as well, however. Therefore, an appropriate data extension technique needs to be applied to the features extracted from observational data sets using a non-parametric bootstrap technique [17], for example. Actual examination of this possibility will be discussed in Section 4.

3. Method

3.1. PLR observation

A single PLR waveform in response to a light pulse of aged people was measured [5]. The stimuli consisted of

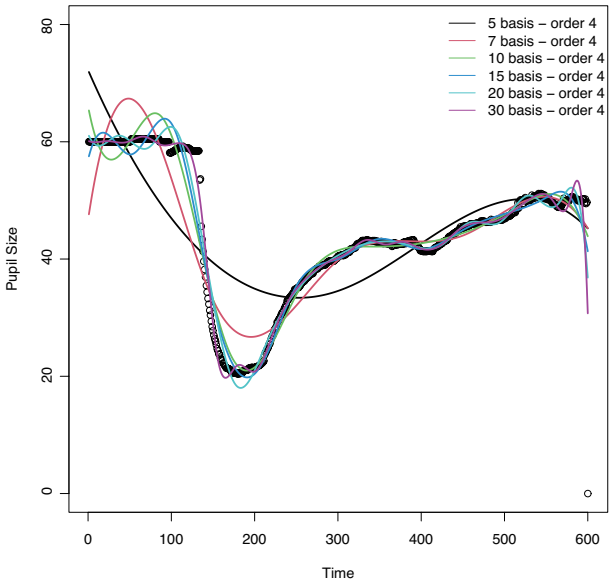

Figure 3. A summation of PLRs for blue light pulses and B-spline representations using $5 \sim 30$ basis functions.

three chromatic lights, red (635nm), blue (470nm) and white (CIE x:0.28, y:0.31), at two levels of brightness (10 and 100 cd/m^2). The two factors, chromatic lights and light intensity, are keys for PLR waveforms. In total, 6 stimulus conditions were labelled as r10, r100, b10, b100, w10 and w100. The duration of observation 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 [5, 18]. PLRs for each stimuli were observed in single trials using a repeated-measure design.

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 (normal control (NC) 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 to participate in the experiment. Informed consent was obtained from all participants prior to the experiment.

Examples of measurements for a healthy individual and for an AD patient are shown in Figures 1 and 2. In these figures, PLRs are illustrated in response to 6 stimuli, namely the 3 colours and two levels of brightness.

3.2. Functional Data Analysis

These waveforms were represented using B-spline basis functions as a technique of functional data analysis (FDA) technique [15, 19]. Figure 3 shows an example of an individual summation signal of PLRs for b10

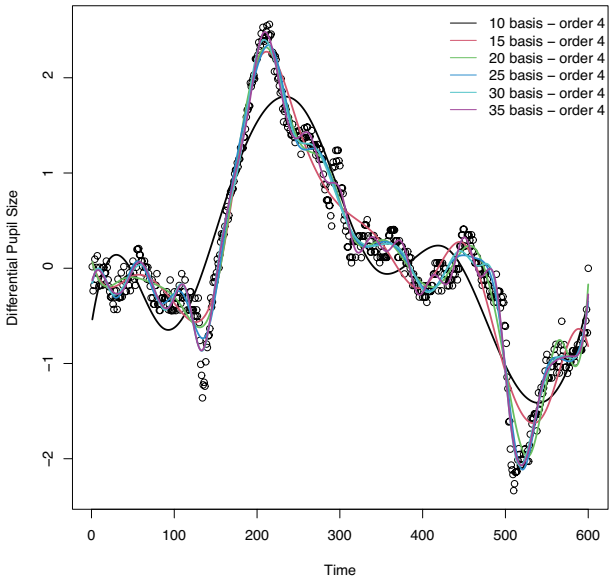

Figure 4. A differential signal of PLRs for blue light pulses between 10 and 100 cd/m^2 and B-spline representations using $10 \sim 35$ basis functions

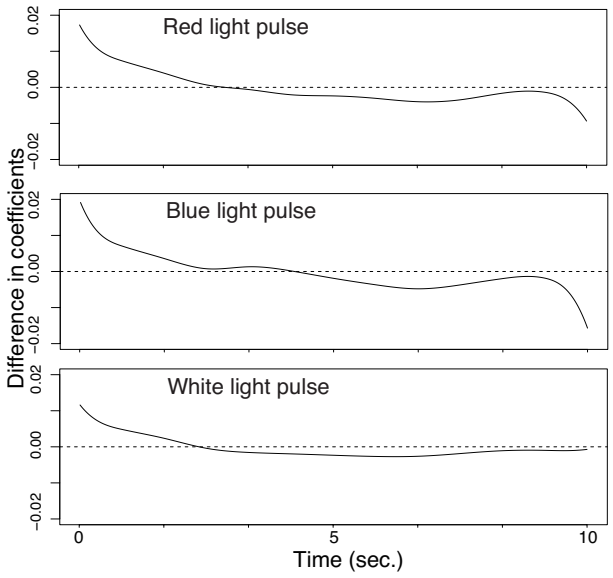

Figure 5. Feature differences for chromatic stimuli with observation time for AD and NC subjects

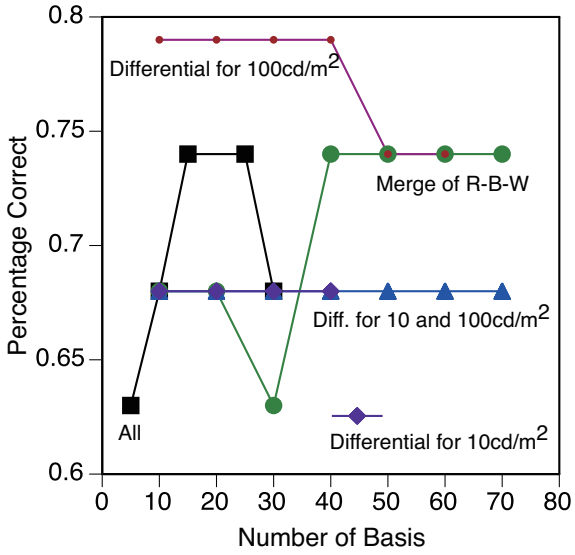

Figure 6. Classification performance for AD and NC participants using trained models, with summation and differentials between chromatic stimuli

and b100, which are blue light pulses (the open circles). The summation signal seems moderated and with less noise. Some B-spline functions are introduced periodically, and the composite signal can represent the PLR waveform. When the number of functions increases, the fitness of the waveform increases, as shown in Figure 3.

A differential signal of PLRs between b10 and b100 is illustrated in Figure 4. As the figure shows however, there is little difference in advance of the light pulse, and the difference is maximised at around the most pupil-constricted time and in the final stage of pupil-restoration. Since the differential signal shows spontaneous changes, noisy waveforms are presented in comparison with the summation signal. The FDA technique is also applied, as a greater number of functions is required to represent the waveform.

The coefficients for each B-spline function which represent the waveform can be a feature set of individual responses. Here, differences between chromatic stimuli or light intensities are processed, and feature sets of PLR waveforms are used for extracting patients with AD.

3.3. Data Extension and Discriminant Analysis

Since the experimental data consists of only 7 AD and 12 NC participants, the number of samples is insufficient to perform discriminant analysis. Here, a data extension technique is applied to the extracted feature set of sampled data using random Gaussian distribution numbers. As a result, 100 samples were generated for each AD and NC group from the statistics of the sampled data such as Gaussian data generation with means and SDs of each group of samples. This generated data set is used for training, and the original measured data is used for testing the trained models. Of course, the training data set and models can be re-generated to extend feature spaces when new experimental data is added. The data spaces of the extracted features of the two groups of participants were trained with a sparse logistic regression function using Elastic-Net with Lasso technique, a variable selection technique [16].

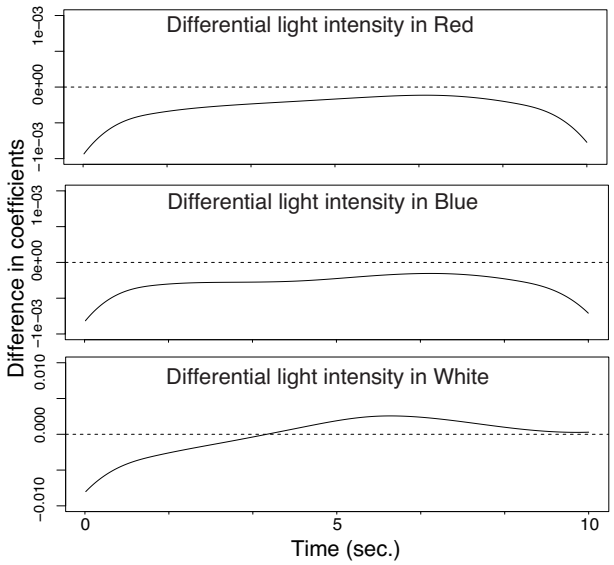

Figure 7. Feature differences for differentials of light intensities with observation time of AD and NC subjects (differences for White light include a wider range than others)

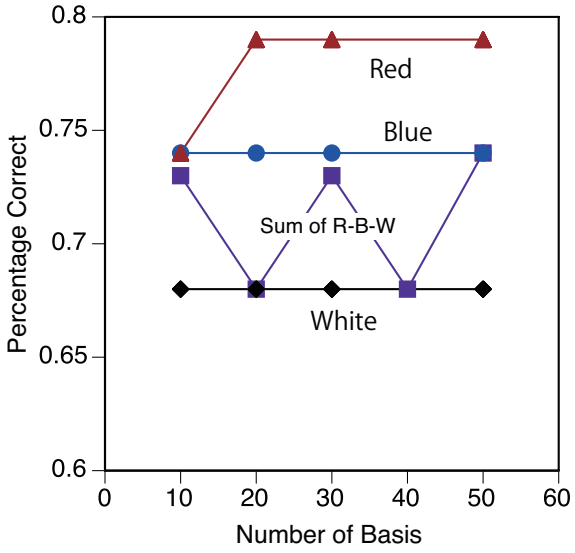

Figure 8. Classification performance of AD and NC participants using trained models with summations and differentials between two light intensities

Because there is very little labelled data for detecting patients with AD, the probability of classification of each participant is calculated using data from their responses. Classification performance of the trained models was evaluated in regards to the number of basis functions using the sampled data set. This testing procedure may provide confirmation of the effectiveness of introducing features.

4. Results

Classification performance of the trained models using AD and NC participants is evaluated as a level of accuracy and as the area under the curve (AUC) of ROC for the sampled data.

4.1. Summation and differentials between chromatic stimuli

The effect of each chromatic stimulus is confirmed in this section. PLRs at the two levels of light intensity were observed, and summation signals for each chromatic light were calculated. These signal features were extracted using the FDA technique and were weighted for classification using Elastic-Net. The temporal changes of feature contributions as coefficient functions [14] for each chromatic stimulus for AD and NC were calculated, as shown in Figure 5. The central dotted line indicates zero, meaning there is no effect on the classification. So, the drawing of a curved line far from zero may possibly be the key to classification. The main difference appeared at the beginning of observations because the pupil sizes of the two groups were different. Some differences appear during the PLR restoration process. In particular, the differences between blue and red light pulses are larger than the differences between white and blue or red light pulses.

Classification performance is summarised in Figure 6. The features are generated along with the number of basis functions using FDA. As shown in Figure 3, a small number of basis (n-basis) such as 10 or 20 is sufficient for the summation signal. For differential signals, many n-basis are required, as shown in Figure 4. The horizontal axis in Figure 6 represents the n-basis for the differential signals. The vertical axis represents the correct rates. When the feature vectors are combined, the number of dimensions for features increased. Therefore, performance has a peak at around 10 to 20 n-basis when all generated features are introduced (All,$AUC = 0.83$). However, combinations of three chromatic stimuli (a merger of R-B-W) produce a plateau when the number of n-basis is between 40 and 70 ($AUC = 0.85$). However, peak performance comes from differentials between chromatic responses ($AUC = 0.88$) for high light intensities ($100cd/m^2$), though the performance of both low light intensity ($AUC = 0.80$) and a combination of two light intensities ($AUC = 0.82$) remains at around the middle level of performance. These results suggest the difference between the level of light intensity may provide the information needed to diagnose patients with AD. Comparing the classification performance using a feature points-based approach provides an approximate value of the $AUC = 0.9$ [5], and the performance of most values for AUC are slightly lower.

Nevertheless, the procedure may be applied to various conditions using summation and differential signals.

4.2. Summation and differentials between stimulus light intensities

Differential signals between the two light intensities (10 and 100 $cd/^2$) are examined, and the temporal changes in feature contributions between AD and NC participants for each chromatic condition are summarised using the same format as shown in Figure 7. The differentials for red and blue light pulses may contribute to classification along with the duration of the observation time.

Classification performance is summarised using the same format in Figure 8. The highest performance is with red light, such as when there are more than 20 n-basis for differentials and 10 n-basis for summation of PLRs at the two intensities of light ($AUC = 0.88$). Conditions using blue light show similar performance ($PC = 0.74, AUC = 0.88$). Other conditions such as combinations including PLRs for white light remained at lower levels of performance.

These results suggest that PLRs for different light intensities or a high level of light intensity with red or blue lights may show better AD classification performance.

5. Summary

This paper presents the effectiveness of differential signals of PLRs for detecting AD patients and NC participants. The experimental conditions consist of three chromatic stimuli and two levels of light intensity. The features of PLR waveforms were extracted using B-spline basis functions as a FDA technique. The number of basis functions was controlled in order to optimise the classification performance. Classification was conducted using a trained Elastic-Net with a data set generated using a data extension technique.

The following results were obtained.

1. A certain number of basis functions for differential signals of PLRs contribute to classification performance more effectively than the functions of summation signals.

2. The differentials of PLRs for the two levels of light intensity (red and blue light pulses) provide better performance than other sets of combinations of PLRs.

As the valid number of participants was too small due to the difficulty of recruiting elderly volunteer participants, a more appropriate set of features should be sampled in order to create a better classification model. Additionally, response differences between left and right eye pupil may provide an information of synchronised reaction of them. The periodical observation and accumulation of the response in daily life may help to manage individual health-care. The procedure should be considered based on the results. These will be the subject of our further study.

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