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Neural Signal Processing of mfVEP Responses from AMD Patients

Yanti Rosli^{1,2}

*Department of Biomedical Science,
Faculty of Allied Health Sciences, Universiti
Kebangsaan Malaysia,
Jalan Raja Muda Abdul Aziz,
Kuala Lumpur 53300, Malaysia.
dr.yanti_rosli@yahoo.com.au*

Xin-Lin, Goh², Andrew James², Ted Maddess²,

*²Centre of Excellence in Visual Sciences,
Research School of Biological Sciences,
Building 46, Australian National University,
Canberra 2602 ACT, Australia
xin-lin.goh@anu.edu.au,
andrew.james@anu.edu.au,
ted.maddess@anu.edu.au*

Abstract

Normal healthy subjects and AMD patients were recorded using 64 EEG channels with a computer based acquisition systems using a pattern-pulse mfVEP. A correctly sized head cap (10/20 layout), was placed over the subjects' head. The Fpz electrode holder was placed directly on the 10% nasion-inion mark. The data are simultaneously sampled at 256 Hz per channel, and collected using the ActiveTwo BioSemi data acquisition software. The Active Ag-AgCl electrodes mounted on the head cap was connected to the Biosemi A/D interface box. The stimulus layout was an 84 region per eye cortically-scaled dartboard comprising 12 sectors and 7 concentric rings, subtending a diameter of 23°; presented dichoptically at 60 Hz frame rate. The 64 electrode channels were held in place with a head cap with a 10/20 layout. Regression models accounting for independent effects were estimated. The Pattern-pulse mfVEP technique is able to record from patients with advance stage AMD.

1. Introduction

Age-related macular degeneration (AMD) has been estimated to affect between 0.7 to 1.9% of the population studied in the United States (The Beaver Dam Eye Study; Wisconsin); Netherlands (Rotterdam) and Australia (Blue Mountain; Sydney and Victoria); [1-4]. It is stated to be the leading cause of irreversible visual loss of individual over 50 years of age in Australia [5, 6]. Consequently, it is a major public health concern given the increase life expectancy, translating AMD into becoming one of the biggest

problems in the next few decades as it has overwhelming effects on quality of life and independence. AMD causes lesions that are often small but have devastating impact, as it causes the loss of retinal photoreceptors in the late stages, ultimately leading towards the loss of visual acuity of the foveal region which is responsible for fine vision. [7-9].

This study was carried out to compare the response from the normal healthy subjects and the AMD patients, using a new type of multifocal VEP (mfVEP) recording technique: the pattern-pulse multifocal VEP [10]. The *multifocal* recording technique was developed by Erich Sutter and co-workers for visual system studies permitting many responses to be estimated within a relatively short period of time providing insights into topographical retinal function. Multifocal methods encompass the simultaneous presentation of independent sequences of stimuli at multiple visual field locations, followed by an analysis method which reduces the measured compound responses into components characteristic of the particular stimulus locations [11]. In mfVEP, the areas of cortex were independently stimulated according a binary m-sequence governing the contrast of each of many stimuli. In this technique, optic pathway conditions can be diagnosed using responses from multiple individual segments of the visual field, therefore allowing topographic visual field deficits to be characterized using measures such as reduced response amplitudes or abnormal latencies. Currently there are only two treatments: argon laser photocoagulation and photodynamic therapy, have been used to curb cvAMD progression rather than to restore vision [12-14]. Hence, a more prudent

approach is to recognise the disease in its earlier stages and treating it then.

2. Methods and data acquisitions

2.1. Subjects selection criteria

Twenty six subjects were recruited in the control group; who had no history of eye diseases, no complaints concerning visual function, best corrected acuity, normal interocular pressure and normal visual field. The age range was 20 to 77 years (mean 39.0 ± 15.8 years, 11 females). AMD patients were recruited from patients seen within the past two years at the Canberra Eye Hospital, Australia. AMD patients included in this exploratory study had diagnoses of both wet and geographic atrophy. Seven patients with wet AMD (cvAMD) in either eye or both eyes (mean age 77.63 ± 11.81 years) participated in the study. None of the subjects had systemic diseases or were on medications (e.g. chloroquine) known to affect retinal function. Patients with other ocular diseases other than AMD were excluded. All subjects were informed of any potential risks prior to participation and gave informed written consent. This research was approved by ANU Human Research Ethics Committee and adhered to the tenets of the Declaration of Helsinki.

2.2. Subject preparation

A cap with 64 electrode channels was placed over the subjects' head. The Fpz electrode holder was placed directly on the 10% nasion-inion mark. Electrode holders on head cap were filled with gel (Signa Gel, Parker) and pin-type active electrodes were used and the contact quality is checked by the offset values in the BioSemi acquisition software (Biosemi Ltd, Amsterdam).

2.3. Multi-modal data acquisition system with active electrodes (ActiveView)

The experimental data are simultaneously sampled at 256 Hz per channel, and collected using the ActiveTwo BioSemi data acquisition software; Activeview. The pin type Active Ag-AgCl electrodes mounted on the head cap was connected to the Biosemi 64 channel A/D interface box. The A/D-box digitized each of the 64 sensory signals with 24 bit resolution and the outputs were sent to the data collection computer. The collected data was buffered and streamed in near real time by data acquisition software (Actiview, BioSemi). The software also

enables all biosignals from the 64 channels to be displayed on-screen in real time.

2.4. Stimulus delivery

The stimuli subtended a diameter of 23° and were presented dichoptically at a 60 Hz frame rate. The stimulus layout was an 84 region cortically-scaled dartboard comprising 12 sectors and 7 concentric rings. The increasing eccentricity of the ring centres were, 1.6° , 3.0° , 4.8° , 7.1° , 10.2° , 14.3° , and 19.8° permitting approximately similar areas of cortical area V1 to be stimulated by each region, generating results of a similar magnitude across eccentricities.

Each recording run lasted for 241.75s; carried out in four segments of average duration 60.94s; with 14505 frames per run. Within each frame, one or more regions could be active 9 (Fig.1). Each 4x4 checkerboard pattern was pulsed on for 33ms with the black checks having a luminance of 1 cd/m^2 , and the white checks having a brightness of 180 cd/m^2 . When these checkerboards were displayed 50% of the time they had one or the other check polarity, and when no checkerboard was present the monitor was maintained at the mean luminance of 90 cd/m^2 . Stimulus markers output by the stimulus computer's parallel port and were recorded in the response file.

Figure 1: Sample of dichoptic stimulus at frame 708; that is delivered concurrently to the left eye (OD, left panel) and the right eye (OS, right panel).

2.5 Data analysis

The continuously recorded data file was transferred to a data analysis environment (Matlab). Data runs were extracted from the continuous file according to the stimulus markers. Portions of the data records containing artefacts were excluded from the analysis. Signals were digitally filtered within a bandpass of 1 to 20 Hz, using a third-order Butterworth filter. Signals were then resample to 240 Hz. The set of 64 scalp electrodes was augmented with a zero signal for the reference channel Fpz, and the average signal over the resultant set was subtracted from each signal, to

give an average-referenced response signal set. Mean responses from all channels over the 84 regions and normal subjects were extracted; and these were compared to mean responses collected at channel POz and from the occipital electrodes channels.

Regression models accounting for independent effects like age, gender, sectors, eccentricities, types of AMD and the interactions between response and subject's age were estimated. We used the multivariate linear model;

$$Y_{[n*m]} = Z_{[n*r]} \beta_{[r*m]} + \varepsilon_{[n*m]} \quad (\text{Eq. 1})$$

where Z is the *design matrix*. Each column of Z consists of the n values of the corresponding variable, for m observations. In this study, $m=1$, and r is the number of fitted coefficients. β is the vector of estimated model parameters characterizing the data that are to be estimated. Vectors for various possible regression models were made that matched the design matrix, one coefficient per vector is fitted, and the error variance were calculated after the regressed variables were extracted and squared; in search for the parsimonious sets of regressors that able to characterize the data well. The simultaneously estimated regression coefficients were examined. The responses (in microvolts) were first transformed to decibels (Eq. 2). The reason to use the log transformation is it even out the variance in the VEP values therefore additive regression models can be fitted to those responses to quantify multiplicative effects [11].

$$\text{dB}_{\text{VEP}} = 20 \log_{10}(nV_{\text{VEP}}) \quad (\text{Eq. 2})$$

A rectilinear layout was used to represent these sets of response waveforms obtained from the 64 electrode-array on a scalp plot matching the dartboard stimulus. The layout is indexed vertically by the polar angle above the horizon of the region's center, from -75° to 75° , and horizontally by the eccentricity in the visual fields (the left or the right of the regions center).

3. Results

The standard data set of the experiment consists of a five dimensional array with the dimensions response delay, electrode channel, stimulus condition, stimulus region in visual field, and the subject/record number. Over the set of 26 normal subjects, averaged over the electrode channels, the RMS strength ranges from 0.01 - $1.48\mu\text{V}$, the grand mean for RMS response strength is $0.17 \pm 0.07\mu\text{V}$. Among the occipital electrode channels, the biggest RMS strength recorded was at location POz; with the mean RMS at electrode POz channel across subjects being $0.23 \pm 0.12\mu\text{V}$. The peaks have amplitudes ranges from 0.01 - 2.53 (overall mean peaks amplitude of $0.29 \pm 0.25\mu\text{V}$, with overall

largest peak at POz had amplitude of $0.24\mu\text{V}$ averaged over regions. The grand mean for SNRs (which was presented as Z_{stat}) acquired over 3864 waveforms (from 46 data sets from 26 subjects, including repeats and 84 regions) at POz is 2.34 ± 0.63 ; 51.37% of them had SNRs greater 2, and 5.01% were greater than 5. In addition, the biggest SNR recorded was a z-score of 14.40. The responses received by the left and the right eyes correspond closely, (Pearson correlation of OS/OD is 0.99).

The response from AMD patients showed a decrease in responses to the inner visual regions, especially in the central eccentricity. Interestingly, not one region showed absence of responses from either OS or OD; although we observed a lag in the waveforms from the OS and OD; or deficits in either waveforms depending on the case. For example, in the case of bilateral cvAMD (Fig. 2), subject 219 (male, 81 years old, OS 6/60, OD 6/36), still shows response from the legally blind eye (due to disciform macular degenerative leakage with haemorrhage) although the response is really small. Response amplitudes from his better eye, OS are bigger in the lower hemifield but show the classic reduced response in the inner three eccentricities in the lower hemifield and at almost all eccentricity in the upper hemifield. Another subject in this category is 227 (female, 77 years old, both cvAMD, deteriorated within 1 year since first noticing changes in her visual field). The response amplitude in this subject is reduced dramatically in almost all eccentricities, both upper and lower visual hemifields.

4. Discussion

The results show that dichoptic stimulation is possible and the responses to the left and the right eye could be recorded successfully in a total of 4 minutes. Signal to noise ratio shows that the response we recorded were at least 1.13 bigger than the noise. Since the data from the normal control subjects and the AMD patients are fitted concurrently in the multiple regression analysis models, we can statistically compare the responses between the groups with minimum error since the compounding factors are removed in the parsimonious model. By fitting the effects of gender and age independently, we know have an unambiguous picture of the other independent effects such as the presence of AMD. So now, through the regression analysis, we can see how much does different sector affects the response on average. Mean response from sectors in the upper hemifield (sectors 2 to 5; sector 1 being the reference sector) was significantly smaller by 0.86 times (in sector 2) than the mean responses (for instance: sector 2, $0.25\mu\text{V}$) whereas the responses

from sectors 8 and 11 is significantly bigger than the actual response (for instance sector 8 is 1.16 times bigger than the mean response, at $0.34\mu\text{V}$). Also with the multiple regression analysis, for the normal control subjects it was found that eccentricity didn't significantly affect the mean responses as initially thought. We found from the regression analysis model that better responses were recorded with number of repeats for subjects regardless of the gender and the age. Similar in any other clinical procedure, it is useful to be repeatable because excessive variability between repeated measurements decreases the procedures ability to detect changes caused by disease. As AMD is a retinal disease that usually involves the macula, deterioration of the macula causes the development of blind spots, blurred or distorted central vision. Although AMD affects central vision, peripheral vision may remain unaffected. Having this in mind, the stimulus for mfVEP used in this study encompassed the macula (ring/eccentricity 1-5; 1.6° , 3.0° , 4.8° , 7.1° , 10.2° respectively) but it also covered more peripheral retina (ring/eccentricity 6-7; 14.3° , and 19.8°). Stimuli presented in eccentricities 6 and 7 were thus outside the anatomically defined macula. Since small stimulation technique like this study is recommended in patients with retinal pathology [15]; therefore one might expect the focal retinal abnormalities in AMD to affect the mfVEP responses from the central retina more than the responses from the peripheral retina as the reductions in the response density and amplitude considered being indicative of photoreceptors or outer retinal changes in AMD and ARM patients. The mean responses of the normal control subjects exhibits waveforms that at all eccentricities (Fig. 3), with slight changes in the amplitude with increasing eccentricity. Among the AMD patients, the amplitude decrease was more dramatic. This may correspond with the pathology of the disease as vascular changes seen in cvAMD may be one of the mechanisms responsible for a more global retinal dysfunction. The focal electrophysiological deficits found in AMD are consistent with the loss of rods and cones [7] in and around the retinal area of AMD that had been reported before [16].

We observe very significant ($p < 0.000$) amplitude depression in the inner four rings in AMD patients where the decreases were all very significant. This concurred to report by Jurkles *et al.* [17] reported that in cvAMD patients the response densities were reduced within the central 5° (in this study, eccentricity 4 is at 4.8°). Interestingly, we found that there are indeed small responses from legally blind eyes, none of the mfVEP waveforms was completely extinguished. This could only mean that this technique is able to stimulate the remaining retinal

neurons of patients who are blind from the end stage photoreceptor generative disease like AMD.

The pattern pulse mfVEP technique could detect these changes remarkably well, and being able to pick up these differences from the different stages of this debilitating disease. In order to investigate this further longitudinal studies are required and should involve a detailed analysis of macular retinal function (spatial and temporal measures) along with classification, extend and location of abnormalities of the pathogenesis of AMD.

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Figure 2: Rectilinear layout of response set of the grand means from AMD subject, including repeats for electrode channel POz; in dichoptic viewing condition, OS and OD superimposed.

Figure 3: Rectilinear layout of response set of the grand means from all the 26 normal subjects, including repeats for electrode channel POz.