Multifocal ERG signal analysis using structural pattern and wavelet packet analysis

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Abstract

Glaucoma is the second-leading cause of blindness worldwide and early diagnosis is essential to its treatment. Multifocal electroretinography (mfERG) takes simultaneous recordings of focal responses from over 100 different retinal regions and uses them to produce topographic representations of retinal response components. Multifocal electroretinography has been shown to be a useful tool for diagnosing glaucoma. In this paper, morphological analysis of the mfERG signal is combined with wavelet packet analysis to perform automatic classification of mfERG signals. By using this method in diagnosis, it is possible to obtain a sensitivity value of 0.98 and a specificity value of 0.85.

Keywords *Glaucoma, mfERG, Neural Network, Wavelet Packets*

1 Introduction

Open-angle glaucoma (OAG) and angle-closure glaucoma affect a large percentage of the population (60.5 million people) and are the second-leading cause of blindness worldwide [1]. In glaucoma, increasing loss of ganglion cell fibres results in progressive optic atrophy with non-reversible visual field loss.

Several approaches using objective measures of glaucomatous neuropathy that do not rely on psycho-physiological or structural testing have been investigated in recent years. One approach has been to use multifocal electroretinography (mfERG) [2], which takes simultaneous recordings of focal responses from over 100 different retinal regions and uses them to produce topographic representations of retinal response components.

Different paradigms of mfERG have been used to assess the retinal function. For instance, the global-flash mfERG was developed to enhance inner retinal response contributions by emphasizing retinal fast-adaptive mechanisms [3]. The global-flash technique, which combines multifocal stimulation with periodic 'global' (full-screen) flashes, is noteworthy for its ability to extract a larger ganglion cell contribution [4].

The most common methods used to analyse the mfERG signal are based on amplitude and latency waveform analysis. For example, in subjects with primary OAG, the amplitudes decrease while the latencies may increase [5].

A previous paper [6] has described how using morphological analysis of the mfERG signal to diagnose glaucoma achieves a sensitivity value of 0.92 and a specificity value of 0.83. Meanwhile, another paper [7] recently proposed a new analysis method based on wavelet packet analysis of global-flash mfERG signals. By reconstructing the third wavelet packet contained in the fourth decomposition level ($ADAA_4$) of the mfERG recording, it is possible to obtain a signal from which to extract a marker in the 60–80 ms time interval. The marker found comprises oscillatory potentials with a negative-slope basal line in the case of glaucomatous recordings and a positive-slope basal line in the case of normal signals. In this case, the sensitivity and specificity values were 0.81 and 0.73, respectively.

This paper presents the initial results of applying both methods when diagnosing glaucoma.

2 Methods

2.1 Database Recordings

This study comprised twenty-five patients diagnosed with OAG and twenty-five control subjects. Abnormal mfERG signals from glaucomatous patients were selected based on their spatial correspondence with abnormal sectors in the Humphrey visual field (HVF) test (defined by a consistent loss of sensitivity of over 10 dB in at least two repeated visual field tests). An abnormal HVF result was characterized by a pattern standard deviation (PSD) and/or corrected pattern standard deviation (CPSD) below the 95% confidence interval, or a glaucoma hemifield test (GHT) result outside the normal limits. A test was considered unreliable if false positives, false negatives or fixation losses exceeded a threshold of 33%.

Each subject underwent a comprehensive ophthalmologic examination, including a review of his/her medical history, measurement of best-corrected

visual acuity, slit-lamp biomicroscopy, measurement of intraocular pressure using Goldmann applanation tonometry, dilated fundoscopic examination and automated perimetry using the 24-2 Swedish interactive threshold algorithm (Carl Zeiss Meditec, Inc). Informed consent was obtained from all participants. The University of Alcalá approved all the protocols and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

All patient recordings were taken using a commercially available multifocal system (VERIS System 5.1, Electro-Diagnostic Imaging, Inc., San Mateo, CA). The stimulus (Fig. 1) consisted of an array of 103 densely packed hexagons tiling the central region of the visual field and about 45 degrees in diameter. The hexagonal stimulus elements were eccentrically scaled to equalize, approximately, the response amplitudes across the stimulated field (stretch factor of 10.46). The stimulus array was presented on a 21-inch monochrome CRT monitor (NEC-FE2111SB) at a video frame rate of 75 Hz. Each step of the ganglion cell response-enhancing stimulation protocol (M-F-O-F-O) consisted of five video frames. In the first frame (M), each stimulus hexagon was either independently flashed (200 cd/m^2) or remained dark (<1.5 cd/m^2) according to a pseudo-random binary m-sequence. After each multifocal stimulus frame (m-frame), the entire stimulus area flashed brightly (F) (100 cd/m^2). The entire stimulus area then remained dark (O) for the next video frame, flashed brightly (F) for another frame and then was dark (O) again in the fifth frame.

The stimulus was viewed through pharmacologically dilated pupils and a Burian-Allen bipolar contact lens electrode was placed on the eye. Signals were amplified with a Grass Neurodata Model 12 amplifier system with a gain of 50,000, band-pass filters (10–300 Hz) and a sampling interval of 0.83 ms (1200 Hz). Recording duration was 190 ms.

A spatial distribution was obtained by regrouping and averaging the 103 hexagons to create a new 56-sector map to simplify analysis and improve the signal-to-noise ratio (Fig. 2). The 56-sector topography chosen is similar to that studied in automated perimetry, the clinical gold standard for visual field assessment.

Glaucomatous mfERG responses were defined as sectors with clearly abnormal ERG waveforms and corresponding interpolated abnormal HVF sectors with a sensitivity loss >10dB. The database included 723 glaucomatous sectors. Recordings from different numbers of patients could contribute to each sector. Sectors 1 and 2 had the least number of contributing records (3 each), while sector 20 had the highest number of records (24). The control database was made up of 1400 sectors (25 controls, one eye per control, 56 sectors per eye).

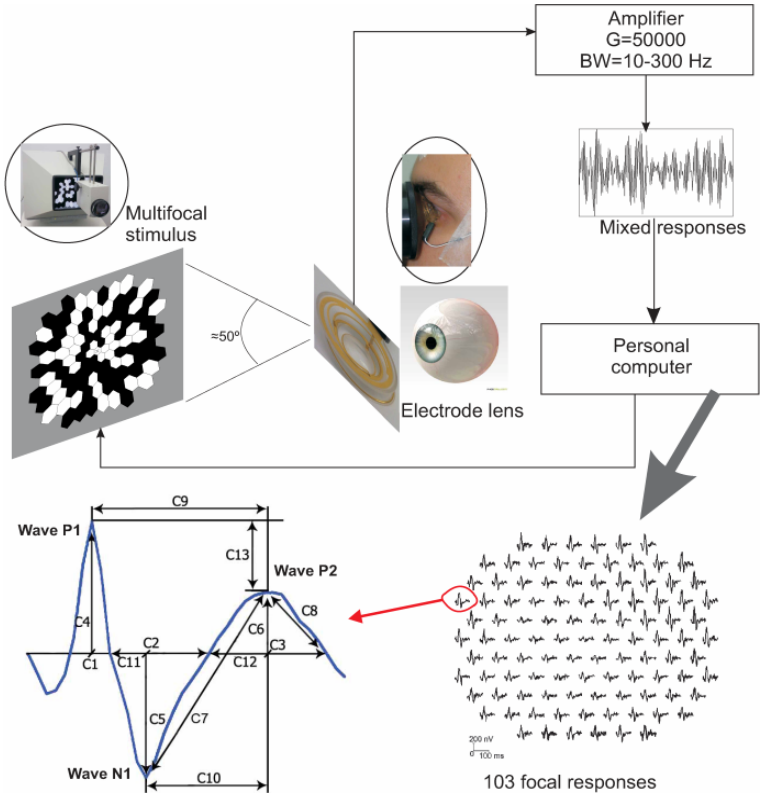

Figure 1: Schematic diagram of an mfERG system and morphological characterization of the waveforms.

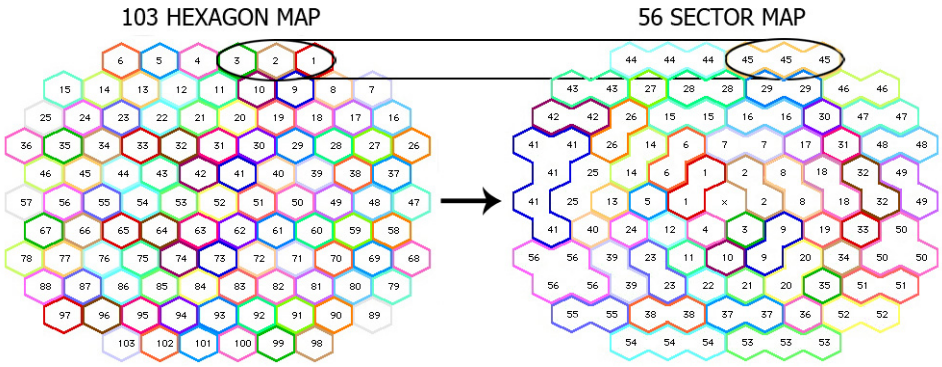

Figure 2: Grouping of the 103 hexagons to form the 56 sectors.

2.2 Structural pattern analysis

The process followed to obtain the signal's morphological characteristics is described in [6]. In summary, the following set of identity patterns (IP) was obtained:

$$IP = [c_1, c_2, ...c_{13}]^T, \quad (1)$$

Where (Fig. 1):

- c_1, c_2 and c_3: IC-P1, IC-N1 and IC-P2 (ms) latencies.
- c_4, c_5 and c_6: amplitude of IC-P1, IC-N1 and IC-P2 (V).
- c_7: linear slope from IC-N1 to IC-P2 (V/ms).
- c_8: linear slope from IC-P2 to the next zero-crossing point (V/ms).
- c_9: IC-P1 to IC-P2 latency (ms).
- c_{10}: IC-N1 to IC-P2 latency (ms).
- c_{11} and c_{12}: IC-N1 and IC-P2 latencies, taken from the previous zero-crossing point to the next zero-crossing point of the wave peak, respectively (ms).
- c_{13}: IC-P1 and IC-P2 amplitude difference (V)

2.3 Wavelet packet analysis

The process followed to obtain the mfERG signal's characteristics using wavelet packet analysis is described in [7]. Study of the analysis group revealed that each mfERG sector signal reconstructed from wavelet packet $ADAA_4$ (the third packet in the fourth level of decomposition) showed a clear repetitive pattern in the time window running from 60–80 ms. This consisted of a 1.5-cycle quasi-sinusoidal waveform section. The $ADAA_4$ packet principally selects the frequency components of the recording between 75–112 Hz. In the case of the signals obtained from control mfERG recordings, the quasi-sinusoidal waveform section shows a rising basal line (0.553 nV/ms ±0.33 SD) that begins with a trough and ends with a peak. Conversely, the signals from glaucomatous mfERG recordings followed a falling basal line (-0.150 nV/ms ±0.27 SD) and the sine wave was inverted in relation to the normal control mfERG sectors.

2.4 Combined analysis

This paper proposes a hybrid system based on a neural-network classifier with the following input vector (IV):

$$IV = [c_1, c_2, ...c_{13}, c_{14}]^T, \quad (2)$$

Where c_{14} (nV/ms) is the slope obtained from analysis of each sector using the method described in section 2.3. A neural network with a radial-basis-function architecture is employed and trained, using the gradient descent learning algorithm, for each of the 56 sectors into which the retina has been divided. The network defines a non-linear relationship between its input/output variables, propagating to the output the samples received at the input (IV) according to the proximity of the inputs to the centres of the exponential functions. The training set comprises 50% of the available healthy sectors and the 443 available glaucomatous sectors. The sectors not used to train the neural network are employed as test elements.

3 Results

This paper demonstrates that individual analysis of mfERG signals may be improved by combining two different analysis methods. Neural network classification combined with the IP responses produced a significant improvement in detection of abnormal sectors.

Abnormal eye responses showed significant and common waveform changes across all the retinal areas (uneven patterns, low energies, slow responses and high-latency components when compared with normal responses). The IPs of glaucomatous eyes showed greater variability and a lower mean value in a significant number of cases. In this regard, the c_7 waveform characteristic was shown to be an excellent common discriminator in relation to early changes in glaucoma.

Table 1 shows the contingency table comparing the

results obtained with this proposed method and those produced by the HVF diagnostic test. The neural network was tested on a group of five glaucomatous patients (one eye per patient, two left and three right eyes, 280 sectors in total, 74 glaucomatous and 206 normal). The sensitivity and specificity of the proposed method is 0.932 and 0.854. The positive predictive value is 0.697 and the negative predictive value is 0.972.

mfERG (sectors)	**Abnormal HVF**	**Normal HVF**
Abnormal mfERG	69 sectors	30 sectors
Normal mfERG	5 sectors	176 sectors
	Sensitivity = 0.932	Specificity = 0.854

Table 1: Results obtained ($p<0.001$, Fisher test).

4 Conclusions

The global-flash mfERG paradigm protocol used in this paper provides a reliable and objective measure of visual loss in glaucomatous patients. This stimulation paradigm extracted a large optic-nerve-head component contribution from the mfERG responses, thereby making it easier to detect waveform abnormalities.

Previous papers, in which structural analysis of the mfERG signal was performed, were able to achieve sensitivity and specificity results of 0.92 and 0.83, respectively. Likewise, wavelet packet analysis produced results of 0.81 and 0.73, respectively. The new method proposed in this paper improves on the earlier results. Nevertheless, these initial conclusions need to be validated by more extensive research.

The proposed method involves exhaustive analysis of the mfERG pattern, producing advantageous results in terms of early glaucoma diagnosis. When compared with other gold-standard glaucoma-diagnosis techniques (automated perimetry), the proposed method detects a higher number of glaucomatous sectors in early stages. This technique enables detection of a large number of abnormal sectors in most of the studied glaucomatous eyes, which may indicate early undetected glaucoma (reduced specificity).

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