BULLETIN OF THE POLISH ACADEMY OF SCIENCES
TECHNICAL SCIENCES
Vol. 53, No. 3, 2005

Analysis of bioelectrical signals of the human retina (PERG) and visual cortex (PVEP) evoked by pattern stimuli

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Abstract. Purpose: to demonstrate the possibility of finding features reliable for more precise distinguishing between normal and abnormal Pattern Electroretinogram (PERG) recordings, in Continuous Wavelet Transform (CWT) coefficients domain. To determine characteristic features of the PERG and Pattern Visual Evoked Potential (PVEP) waveforms important in the task of precise classification and assessment of these recordings.

Material and methods: 60 normal PERG waveforms and 60 PVEPs as well as 47 PERGs and 27 PVEPs obtained in some retinal and optic nerve diseases were studied in the two age groups (≤ 50 years, > 50 years). All these signals were recorded in accordance with the guidelines of ISCEV in the Laboratory of Electrophysiology of the Retina and Visual Pathway and Static Perimetry, at the Department and Clinic of Ophthalmology of the Pomeranian Medical University. Continuous Wavelet Transform (CWT) was used for the time-frequency analysis and modelling of the PERG signal. Discriminant analysis and logistic regression were performed in statistical analysis of the PERG and PVEP signals. Obtained mathematical models were optimized using Fisher $F(n1, n2)$ test. For preliminary evaluation of the obtained classification methods and algorithms in clinical practice, 22 PERGs and 55 PVEPs were chosen with respect to especially difficult discrimination problems ("borderline" recordings).

Results: comparison between the method using CWT and standard time-domain based analysis showed that determining the maxima and minima of the PERG waves was achieved with better accuracy. This improvement was especially evident in waveforms with unclear peaks as well as in noisy signals. Predictive, quantitative models for PERGs and PVEPs binary classification were obtained based on characteristic features of the waveform morphology. Simple calculations algorithms for clinical applications were elaborated. They proved effective in distinguishing between normal and abnormal recordings.

Conclusions: CWT based method is efficient in more precise assessment of the latencies of the PERG waveforms, improving separation between normal and abnormal waveforms. Filtering of the PERG signal may be optimized based on the results of the CWT analysis. Classification of the PERG and PVEP waveforms based on statistical methods is useful in preliminary interpretation of the recordings as well as in supporting more accurate assessment of clinical data.

Key words: electrophysiology, visual system, Pattern Electroretinogram, PERG, Pattern Visual Evoked Potential, PVEP, Continuous Wavelet Transform, CWT, signal classification, discriminant analysis.

1. Introduction

In the paper the results of analysis of two kinds of bioelectrical signals arising in the human visual system are presented. These signals, very important in clinical electrodiagnostics in ophthalmology, are: Pattern Electroretinogram (PERG) and Pattern Visual Evoked Potential (PVEP) [1,2]. Both signals are bioelectrical responses of the retina and visual cortex evoked by a specific optical stimulus, the "pattern" – alternating black and white checkerboard or grating, commonly presented on a CRT monitor. Total, overall luminance of the stimulus remains constant, what results in elimination of stray light effects. From the technical point of view, this type of stimulation represents a local contrast phase modulation with a defined spatial and temporal frequency, expressed in cycles/deg and reversals per second (rev/s, rps), respectively. Both the spatial and temporal characteristics influence the shape of the PERG and PVEP waveforms. Because of the features of this type of stimulus, different from a simple, "primitive" flash of light (evoking Flash Electroretinogram – FERG and Flash Visual Evoked Potential – FVEP) the PERG and PVEP responses reflect activity of neuronal structures involved in image information processing in the visual system. Figure 1 shows the origin of most important bioelectrical signals with their major components – particular "waves", in the structures of retina and visual pathway [2,3]. Abbreviations not explained earlier in the text are as follows: EOG – Electro-Oculogram, OPs – Oscillatory Potentials (extracted from the FERG), mfERG (multifocal ERG) and mfVEP (multifocal VEP) – new methods of mapping electrical activity recorded from the retina and visual cortex evoked by flash or pattern, using sophisticated techniques of stimulation and signal processing [2].

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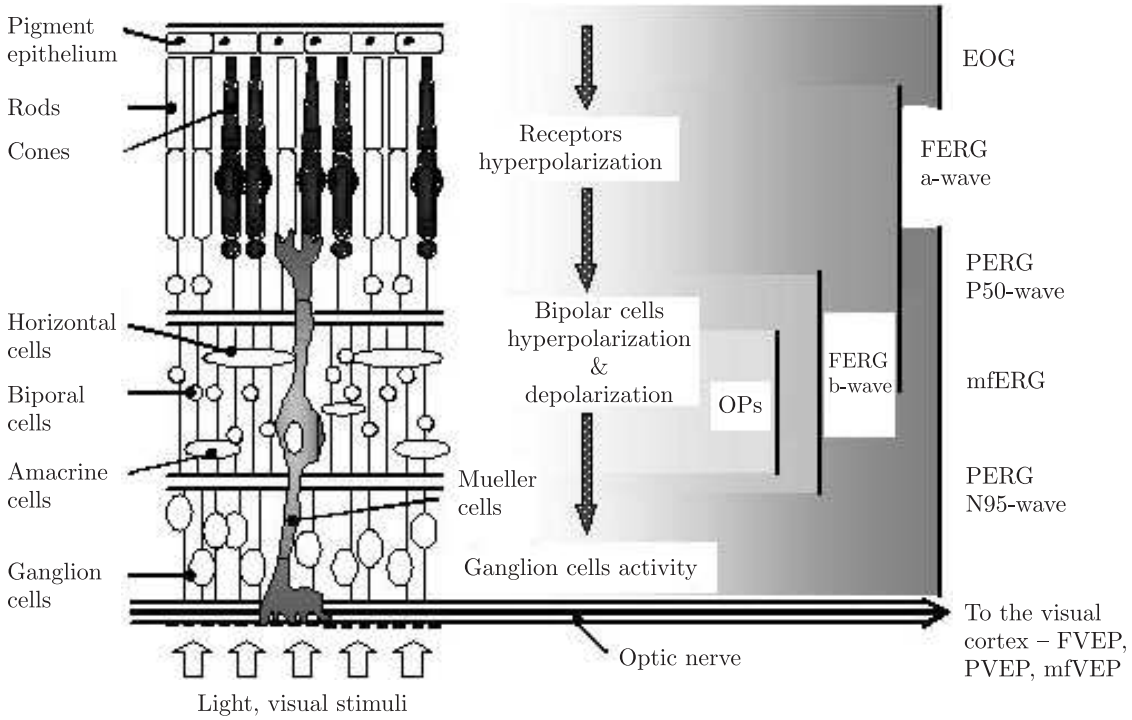

Fig. 1. A schematic diagram of neural cell structures of the human retina and origin of the most important bioelectrical signals arising in the visual system (explanations in the text)

Pattern Electroretinogram (PERG) is recorded from the human retina with a corneal contact electrode. PERG signal originates in the retinal ganglion cells as well as neighboring inner retinal structures [1,2,4]. Particular waves reflect the electrical activity of different neural structures involved in visual information processing and are used in assessment of their function. Three characteristic PERG waves are called N35, P50 and N95. The letters "P" and "N" stand for positive and negative components respectively, whereas the numbers correspond to the approximate time (in milliseconds) when particular components appear – the latency or the peak implicit time.

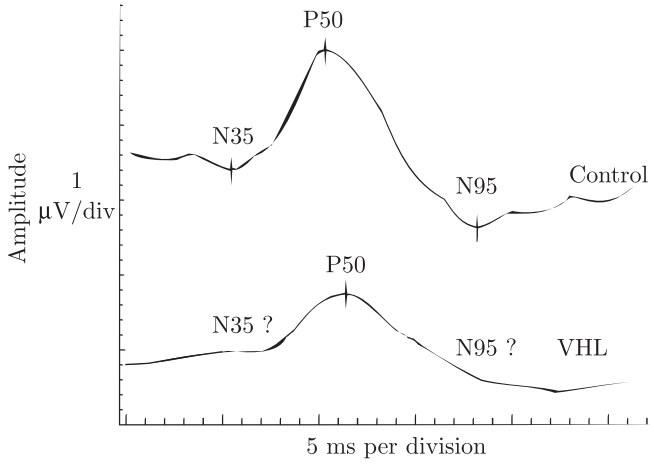

Fig. 2. An example of PERG signals: normal and abnormal, in the von Hippel-Lindau (VHL) disease (after Ref. 8)

On the other hand, Pattern Visual Evoked Potential (PVEP), reflecting the functional state of the pathway ranging from the retina (mainly ganglions) through optic nerve to the visual cortex, is registered with conventional EEG electrodes located in the occipital region (O_Z, O_1 or O_2 according to the International 10–20 System [2,5]). Characteristic waves of the PVEP signal morphology are called N75, P100 and N135, with similar to PERG meaning of the letters and numbers.

Both PERG and PVEP signals are very important in clinical electrophysiology of vision as well as in neuro-ophthalmology [1,2,4–6]. They are useful in diagnostics of the functional state of the retina (macular region), optic nerve and cortex – in detecting, confirming or excluding particular diseases. Analysis of both signals provides valuable information in differentiation between macular and optic nerve dysfunction.

The PERG and PVEP tests – as some other important electrophysiological examinations in ophthalmology – are standardized by the International Society for Clinical Electrophysiology of Vision (ISCEV) [4,5]. According to these standards clinical evaluation of the PERG and PVEP recordings is based on measurement of latencies and amplitudes of particular waves and comparing them with the normal values of a particular electro-ophthalmology lab (normal values should be obtained individually in each lab). Unfortunately, the PERG and PVEP are not easy-to-run electrophysiological tests and even in experienced labs normal values show usually big scatter of results. Signal variability [7] cannot be neglected too. Standard measurement procedures of waveform parameters also lead to significant errors. In many cases it is difficult to lo-

calize the waveform peaks precisely (see Fig. 2 as an example of unclear N95-wave in the PERG recording [8], a typical situation in numerous patients), so the standard method of analyzing the PERG and PVEP parameters in time-domain is inaccurate. This disadvantage affects reliability of these important electrophysiological tests in clinical practice.

In order to improve the diagnostic efficiency and value of the PERG and PVEP tests, the author and co-workers aimed at applying different methods of signal analysis. First goal was to demonstrate the possibility of finding features reliable for more precise distinguishing between normal and abnormal PERG recordings, in the Continuous Wavelet Transform (CWT) coefficients domain. The WT method (Continuous – CWT as well as Discrete – DWT) has already shown its efficiency in analysis, compression and de-noising of some biosignals of complex morphology [9–11]. As far as bioelectrical signals of the visual system are concerned, the wavelet methods have been rarely used up to the present [12–18]. Another approach was based on applying statistical methods in analysis of the PERG and PVEP signals. The goal of this attempt was to determine characteristic features of the waveforms which could be useful in the task of precise classification and clinical assessment of these recordings.

2. Material and methods

In both approaches the recordings collected in the Department and Clinic of Ophthalmology of the Pomeranian Medical University were analyzed. 60 normal PERG and 60 normal PVEP waveforms as well as 47 PERGs and 27 PVEPs obtained in some retinal and optic nerve diseases (for example: macular dystrophies – mainly Stargardt's disease, glaucoma, demyelinative and ischaemic optic neuropathies, pituitary tumors) were studied in the two age groups: ≤ 50 years, > 50 years. All these signals were recorded in accordance with the guidelines of ISCEV [2,4,5] in the Laboratory of Electrophysiology of the Retina and Visual Pathway and Static Perimetry. The recordings were obtained with the systems UTAS-E 2000 (LKC Inc., USA) and RetiPort/RetiScan (Roland Consult, Germany).

Continuous Wavelet Transform (CWT) from the MATLAB package was used for the time-frequency analysis and modeling of the PERG signal.

Discriminant analysis and logistic regression were performed in statistical analysis of the PERG and PVEP signals. Obtained mathematical models were optimized using Fisher $F(n1, n2)$ test. Commercially available tools from the STATISTICA package were used.

For preliminary evaluation of the obtained classification methods and algorithms in clinical practice, 22 PERGs and 55 PVEPs were chosen with respect to especially difficult discrimination problems ("borderline" – with respect to at least one parameter – recordings).

3. Results

3.1. Wavelet analysis of the PERG signal – first experiments. For the purpose of the first investigation [14], 15 normal PERG waveforms and 7 recordings obtained in some precisely diagnosed retinal diseases were chosen. The recordings were obtained with the LKC's UTAS-E 2000 (USA) system. In the abnormal PERGs, P50-wave latency was increased (4 recordings) as well as N95-wave latency (3 recordings). Three different wavelets were used in the preliminary experiments: Morlet, 1st and 2nd (the so-called Mexican Hat – MH) derivative of the Gauss function. A sample result of CWT analysis is shown in Fig. 3.

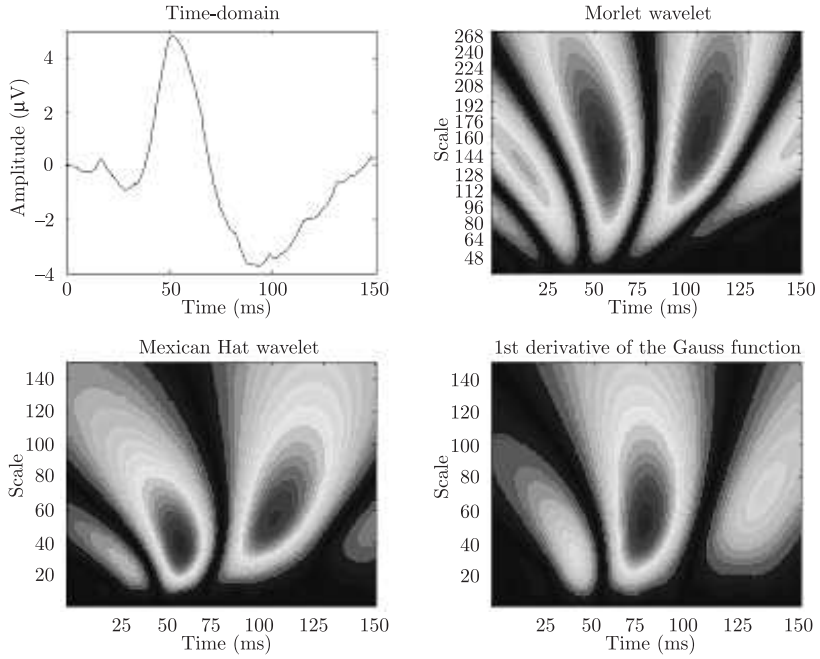

Fig. 3. Comparison of CWT results for the same PERG waveform (with three different wavelets, after Ref. 14)

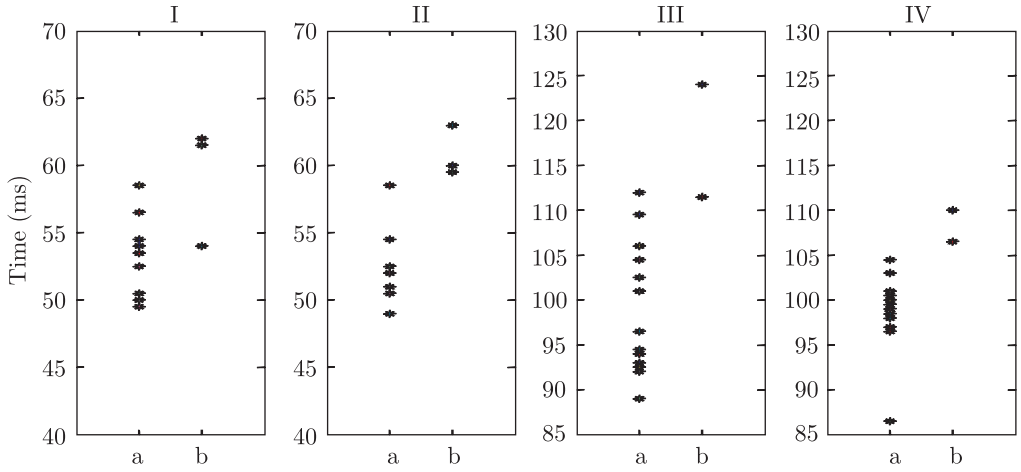

Fig. 4. Comparison of P50-wave and N95-wave latencies: a – normal, b – abnormal waveforms; I – P50 (time method), II – P50 (time-scale method), III – N95 (time method), IV – N95 (time-scale method); some points overlap: group b should have 4 points (I, II) and 3 points (III, IV); MH wavelet was used (after Ref. 14)

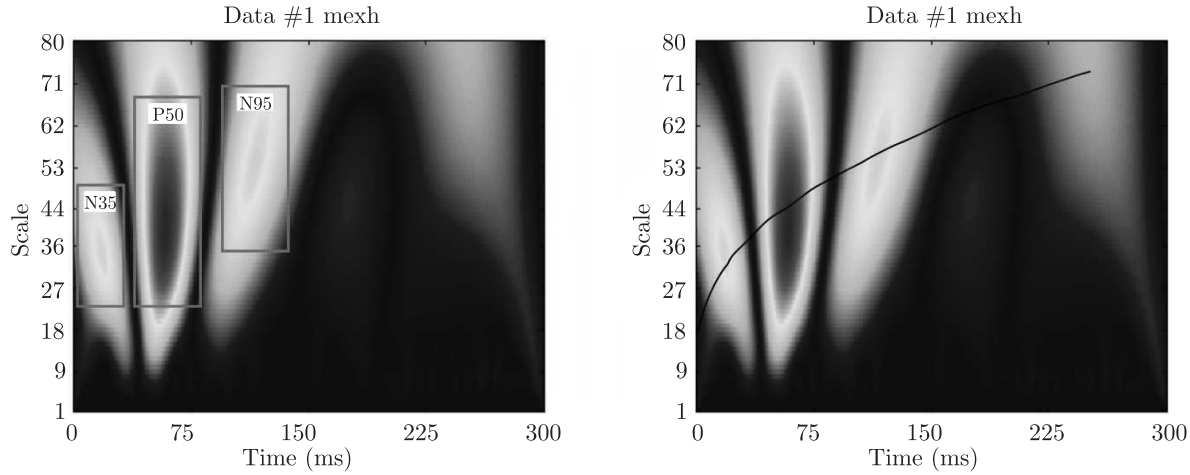

Fig. 5. Curvilinear "section" across the three maxima (for N35, P50 and N95) of signal energy distribution (after Refs. 15,16)

Mexican Hat wavelet was chosen for further analysis – this function was most accurate in detecting required features (that is time-scale images of N35-wave, P50-wave and N95-wave latencies). Comparison between the proposed method using CWT and traditional, time-domain based analysis, shows that determining the maxima and minima (which were obtained from the CWT representation for a chosen level of scale, equal to 50) of the PERG waves may be achieved with better accuracy – see Fig. 4.

This improvement becomes especially evident in waveforms with unclear peaks (like N95) as well as in noisy signals. Thanks to more precise assessment of latencies, separation between normal and abnormal waveforms is improved.

3.2. Wavelet analysis of the PERG signal – further studies. Further steps of analysis [15,16] were performed with a new set of data obtained in the Department and Clinic of Ophthalmology with the RetiPort/RetiScan system (Roland Consult, Germany) in 60 eyes of healthy subjects, in 2 age groups.

The investigations were aimed at comparing the values of the N35-wave, P50-wave and N95-wave latencies, which were calculated traditionally in time domain and are used as normal values in the Clinic, with those derived from the time-scale representation of the recorded PERGs.

In Figs. 5 and 6 the way of determining peak latencies is shown, as well as a "virtual normal PERG representation" in the CWT coefficients domain. It was obtained from the curvilinear "section" drawn across the three maxima – the concentration of signal energy). Comparison of latency values for both methods and both age groups is presented in Table 1. Improvement of "consistency" of the normal values obtained with the CWT method is clearly seen, especially for the N95-wave latency (bold font). This is a very important result because traditional measurements of the N95-wave latency are difficult and often lead to significant errors.

Another interesting result of the analysis is shown in Fig. 6 – approximate dominant frequencies of the three PERG waves were calculated from the CWT maps. Based upon these values it is possible to design an optimal filter for the PERG signal – a bandpass filter with time-varying central frequency.

Table 1
Comparison of latency values for both methods and both age groups (after Refs. 15, 16)

Time-domain method							
Group 1 ($\leq$ 50 years)				Group 2 ($>$ 50 years)			
Latency	Mean	SD	SD/mean	Latency	Mean	SD	SD/mean
N35	27.52	2.39	0.087	N35	28.87	2.01	0.070
P50	51.14	2.57	0.050	P50	52.62	3.61	0.069
N95	104.32	4.53	0.043	N95	104.27	8.06	0.077
CWT method (Mexican Hat)							
Latency	Mean	SD	SD/mean	Latency	Mean	SD	SD/mean
N35	18.06	1.60	0.088	N35	19.22	2.08	0.108
P50	56.25	2.44	0.043	P50	56.80	3.37	0.059
N95	116.02	2.20	0.019	N95	113.52	3.27	0.029

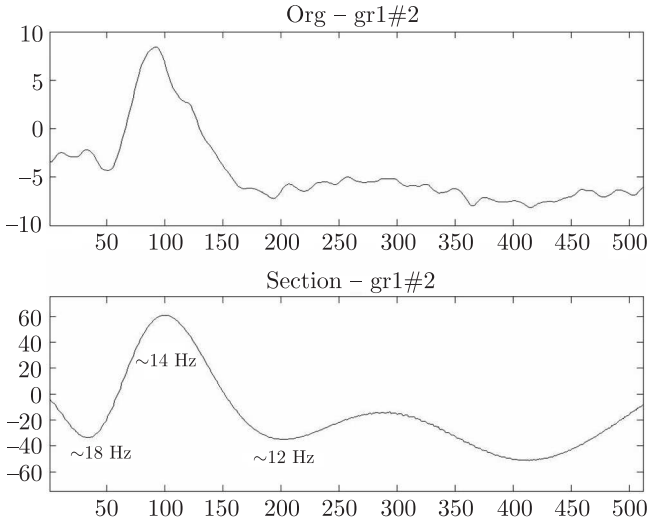

Fig. 6. Example of a normal PERG waveform and its representation obtained from the curvilinear "section" across the CWT map (numbers of samples on the abscissa, CWT coefficients on the ordinate) (after Refs. 15,16)

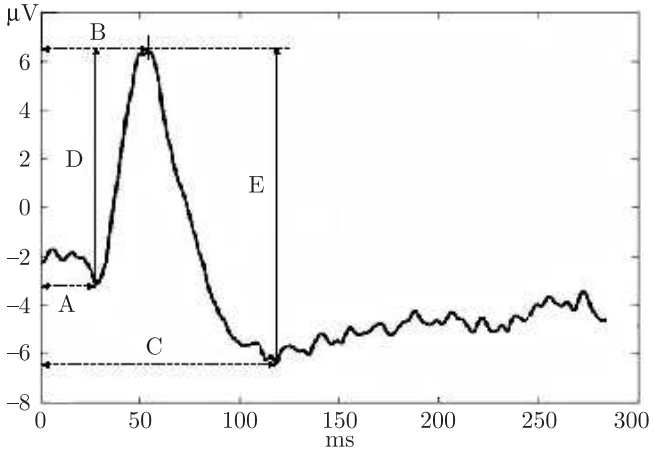

Fig. 7. Characteristic parameters of a PERG recording (after Refs. 19,20)

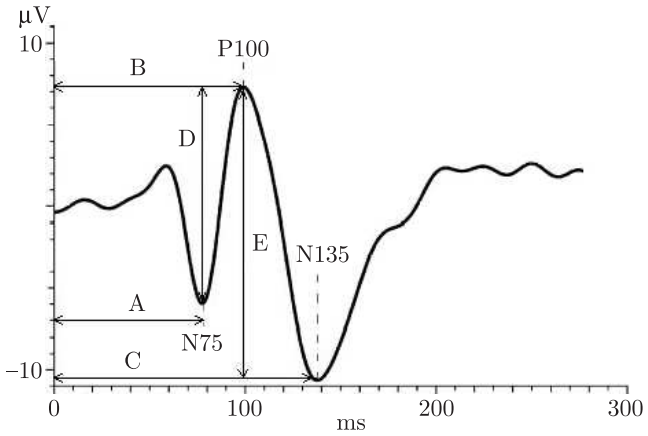

Fig. 8. Characteristic parameters of a PVEP recording (after Ref. 20)

3.3. Statistical analysis of the PERG and PVEP signals. In the statistical analysis [19,20] several parameters characteristic of both signals morphology were determined. These characteristic values are shown in Figs. 7 and 8 and explained in Table 2.

Table 2
Parameters of the PERG and PVEP signals – explanation of symbols used in Figs. 7 and 8

Signal	Latencies of waves (ms)			Amplitudes of waves (μV)	
	A	B	C	D	E
PERG	N35	P50	N95	P50	N95
PVEP	N75	P100	N135	N75-P100	P100-N135

PERG results. Some other parameters for PERGs analysis were obtained by calculations: $D \times E$ and E/D (product and quotient of the amplitudes, respectively). Also the dichotomic variable "AGE" was used (equal to "1" for the younger group and "2" for the older one). The grouping variable, assumed *a priori*, was "N" (equal to "0" for normal waveforms and "1" for abnormal recordings).

The columns of the matrix used for performing analysis were constituted by the described above values, and the rows – by 107 tested PERG waveforms (60 normal and 47 abnormal).

In the study [19,20] the discriminant analysis was chosen as a classification method. In this analysis discriminant functions are derived depending on the considered mathematical model (similar to linear equations of multiple regression). Most important appears to be the choice of independent variables or their elimination in consecutive steps of analysis. The model is evaluated by the Fisher test $F(n1, n2)$, thus may be optimized. Performing statistical calculations and different analyses for complete matrix, for all rows, is a standard procedure.

After running series of analyses and calculations it became evident that for efficient classification of the PERG waveforms, a row-based division of the matrix was necessary. The proper solution was obtained thanks to discovering the determining role of $D \times E$ variable in the matrix division, with supplementary role of E/D variable in the classifying function (this ratio of amplitudes N95/P100 is used in clinical assessment of PERGs, according to the ISCEV guidelines [4]).

The main matrix "M" was constituted by 76 PERG waveforms with:

$$D \times E \geq 53.6\ (\mu\mathrm{V}^2)$$

The variable determining "state" of the particular waveform in this case was E/D:

N = 0 (normal PERG)	if	$E/D \geq 1.135$
N = 1 (abnormal PERG)	if	$E/D < 1.135$

Evaluation of the model: $F(1, 74) = 211.56$, $p < 0.1\ E-4$.

Supplementary matrix "S" consisted of 31 PERG waveforms with:

$$D \times E \leq 51.5\ (\mu\mathrm{V}^2).$$

Classifying function for this matrix was dependent from two variables: E (amplitude of the N95-wave) and AGE:

$$N = -78.331 + 8.662 \times E + 46.762 \times \mathrm{AGE}.$$

If the value of variable N is greater than 50 (null hypothesis confirmed) – the waveform is classified as normal. Evaluation of the model: $F(2, 28) = 69.85, p < 0.1\ E-4$.

The above results obtained in PERG analysis may be used as a simple predictive model for classifying "unknown" PERG waveforms. With this algorithm, implemented as EXCEL formulae, a preliminary clinical evaluation was performed. 22 PERG recordings were chosen and assessed by an experienced clinician. 18 waveforms were "borderline" cases in which the diagnostic decision was uncertain. The results of algorithmic classification of these 22 PERGs were compared with the clinician's decisions (Table 3). In 6 cases the model proved effective in supporting the uncertain, doubtful decisions ("more precise, decisive" classifications). The classification model was denoted as "107" because of the number of PERG waveforms analyzed at this stage.

In the next step 79 PERG waveforms were added to the database and statistical analysis similar to above described was performed. The model, now denoted as "186", was modified:

The main matrix "M" was constituted by 150 PERG waveforms with:

$$D \times E \geq 36.3\ (\mu\mathrm{V}^2)$$

The variable determining "state" of the given waveform in this case was again E/D:

N = 0 (normal PERG)	if	$E/D \geq 1.135$
N = 1 (abnormal PERG)	if	$E/D < 1.135$

Evaluation of the model: $F(1, 148) = 358.76, p < 0.1\ E-14$.

Supplementary matrix "S" consisted of 36 PERG waveforms (all abnormal) with:

$$D \times E < 36.3\ (\mu\mathrm{V}^2)$$

The obtained classification model "186" was thus simplified in comparison with the former one; the same can be said about the calculations algorithm.

Table 4 demonstrates the results of applying this algorithm to the same set of PERGs that was used previously for preliminary clinical evaluation of the "107" model. This time there were no false classifications.

Table 3
Preliminary clinical evaluation, PERG – model "107"

Model/No. of waveforms	Classifications		
	In agreement with clinician's diagnostic decision	More precise, decisive	False
"M" / 13	9	4	–
"S" / 9	6	2	1*

* – Increased latency of the N95-wave was not detected

Table 4
Preliminary clinical evaluation, PERG – model "186"

Model/No. of waveforms	Classifications		
	In agreement with clinician's diagnostic decision	More precise, decisive	False
"M" / 16	11	5	–
"S" / 6	5	1	–

PVEP results. Statistical analysis of the PVEP [20] was performed first on the set of 60 normal and 27 abnormal waveforms, resulting in a model "87". In this model, the "state" of a given waveform was dependent only from two variables: C (latency of the N135-wave) and D (amplitude N75-P100). This time a simple regression equation was used for discrimination between normal and abnormal PVEPs:

$$N = -2.729 + 0.020 \times C - 0.010 \times D.$$

If the calculated value of dependent variable N is below 0.5 – a given PVEP is classified as normal. The EXCEL formula corresponding to this model was used in preliminary clinical evaluation of its classifying efficiency. In the experiment, 21 PVEP various waveforms ("borderline" recordings included) were assessed in the same way that in the case of PERGs. The results of the comparison are shown in Table 5.

Table 5
Preliminary clinical evaluation, PVEP – model "87"

No. of waveforms	Classifications		
	In agreement with clinician's diagnostic decision	More precise, decisive	False
21	13	2	6

It was clear that the "87" model was too simple and detailed analysis showed that the false classifications corresponded to the uncertain, "borderline" PVEPs. So in the next step the PVEP database was supplemented by these additional 21 recordings and a new model "108" was elaborated as a result of statistical analysis. It occurred that for proper classification of the PVEPs in the new set of data it was necessary to introduce third variable, B (latency of the P100-wave). It is a very important observation because this latency shows abnormalities in numerous retinal and optic nerve diseases [2]. The following "108" model was obtained:

$$N = -1.559 + 0.018 \times B - 8.570 \times D/C.$$

If the calculated value of dependent variable N is below 0.5 – a given PVEP is classified as normal. The clinical evaluation of the "108" model was performed using a new set of 34 PVEP waveforms (with a significant contribution of "borderline" cases). This time the results, shown in Table 6, are much more satisfactory.

Table 6
Preliminary clinical evaluation, PVEP – model "108"

No. of waveforms	Classifications		
	In agreement with clinician's diagnostic decision	More precise, decisive	False
34	21	12	1

4. Conclusions

CWT based method of the PERG signal analysis is efficient in more precise measurement of the latencies of particular waves (especially the N95-wave), improving separation between normal and abnormal waveforms and accuracy of clinical PERGs assessment. Based on the obtained results of analysis of the PERG recordings, digital filtering of these signals may be optimized.

The results of statistical analysis of the PERG and PVEP signals show the possibility of creating classification algorithms based on simple mathematical models. Classification of the PERG and PVEP waveforms based on statistical methods is useful in preliminary interpretation of the recordings as well as in supporting clinical decision-making in "borderline" cases, for more accurate assessment of clinical data.

REFERENCES

[1] G.E. Holder, "Pattern electroretinography (PERG) and integrated approach to visual pathway diagnosis", *Progr. in Retinal and Eye Res.* 20 (4), 531–561 (2001).

[2] O. Palacz, W. Lubiński, and K. Penkala, *Clinical Electrophysiology of the Visual System* (in Polish). OFTAL, Warszawa, 2003.

[3] M.F. Marmor, G.E. Holder, M.W. Seeliger, and S. Yamamoto, "Standard for clinical electroretinography (2004 update)", *Doc. Ophthalmol.* 108, 107–114 (2004).

[4] M. Bach et al. "Standard for pattern electroretinography", *Doc. Ophthalmol.* 101, 11–18 (2000).

[5] V. Odom et al., "Visual evoked potentials standard (2004)", *Doc. Ophthalmol.* 108, 115–123 (2004).

[6] M. Bach and T. Meigen, "Do's and Don'ts in Fourier analysis of steady-state potentials", *Doc. Ophthalmol.* 99, 69–82 (1999).

[7] T. Otto and M. Bach, "Retest variability and diurnal effects in the pattern electroretinogram", *Doc. Ophthalmol.* 92, 311–323 (1997).

[8] W. Lubiński, K. Krzystolik, C. Cybulski, Z. Szych, K. Penkala, O. Palacz, and J. Lubiński, "Retinal function in the von Hippel-Lindau disease", *Doc. Ophthalmol.* 106, 271–280 (2003).

[9] M. Akay, *Time Frequency and Wavelets in Biomedical Signal Processing*, Wiley, 2000.

[10] M. Unser and A. Aldroubi, "A review of wavelets in biomedical applications", *Proc. IEEE* 84 (4), 626–638 (1996).

[11] T. Rogala, A. Brykalski, and K. Penkala, "Certain applications of the wavelet transform in biomedical engineering", *XXVI ICSPETO*, Gliwice – Niedzica 2, 415–418 (2003).

[12] H. Drissi, F. Regragui, J.P. Antoine, and M. Benouna, "Wavelet transform analysis of visual evoked potentials", *Proc. UCL-IPT Conference*, (1998).

[13] A.C. Fisher, R.P. Hagan, A. Mackay, and M.C. Brown, "Removal of the frame break-through artefact in PRVEP recordings using a system of wavelet decomposition", *2^{nd} Annual Meeting of the British Society for Clinical Electrophysiology of Vision (BriSCEV)*, Liverpool, p.102 (2004).

[14] K. Penkala, T. Rogala, and A. Brykalski, "Analysis of the pattern electroretinogram signal using the wavelet transform", *48 Internationales Wissenschaftliches Kolloquium*, Ilmenau, 145–146 (2003).

[15] K. Penkala, T. Rogala, A. Brykalski, W. Lubiński, and O. Palacz, "Wavelet approach to the PERG analysis and processing", *2^{nd} Annual Meeting of the British Society for Clinical Electrophysiology of Vision (BriSCEV)*, p.103, Liverpool (2004).

[16] K. Penkala, T. Rogala, A. Brykalski, and W. Lubiński, "Wavelet transform in analysis of the pattern responses of the human retina (pattern electroretinogram – PERG)", *4^{th} European Symposium on Biomedical Engineering*, Patras, Greece., (2004).

[17] T. Rogala, A. Brykalski, and K. Penkala, "Wavelet compression of electroretinogram – preprocessing for neural classification purposes", *Proc. MMAR'04* 1, 641–646 (2004).

[18] T. Rogala, A. Brykalski, and K. Penkala, "Certain Aspects of bioelectrical signal smoothing" *Measurements, Automatics, Control* – PAK (9), 21–25 (2004).

[19] K. Szlachta, K. Penkala, A. Brykalski, and W. Lubiński, "Statistical analysis of the pattern electroretinogram (PERG) signal", *Proc. 6th International Conference on Unconventional Electromechanical and Electrical Systems UEES'04* 3, 927–930 (2004).

[20] K. Penkala, W. Lubiński, K. Szlachta, and D. Karczewicz, "Discriminant analysis of PERG and PVEP – mathematical models, preliminary clinical evaluation", *International Society for Clinical Electrophysiology of Vision (ISCEV) XLIII Annual Symposium*, Glasgow, 23–27.08.2005 (to be published).