Detection of Visual Field Defect Using Topographic Evoked Potential in Children

P.K.H. Wong *
R. Bencivenga **
J.E. Jan†
K. Farrell††

**B.Eng., M.D., F.R.C.P. (C)*
***Ph.D.*
†M.D., F.R.C.P. (C)
††M.B., Ch.B., D.C.H., F.R.C.P. (C)
Department of Paediatrics, U.B.C.
Department of Diagnostic Neurophysiology
B.C. Children's Hospital, Vancouver

1. Introduction

The interpretation of visual evoked potentials (VEP) suffers from a lack of objectivity due to several causes. First there is as yet no good biological model explaining the relation between the physiological activities occurring in the brain and the voltage variations measured during the VEP. This means that no mathematical standard for a "normal" reading has been set, nor a normal range of variation against which to test a VEP under investigation. There are certain features whose presence or absence are considered relevant to the analysis, like peak morphology and latency features, but these are difficult to code mathematically and it is not clear at all what their statistical distributional properties are, both in the healthy population and in specific types of illnesses.

> In this study we have therefore tried to concentrate on methods which may be justified on a theoretical basis, accepted on an empirical one, and could be treated in a manner as objectively as possible.

Other features which may seem more amenable to mathematical coding, like the latency and amplitude of the main occipital positive peak, need a subjective element for their identification and, moreover, have proved to have variable discrimination power in the study of patients with visual field defects[1]. Increasing the number of scalp electrodes has provided additional information of the relationship of electrical activity between different brain regions, and has been found useful[2].

In this study we have therefore tried to concentrate on methods which may be justified on a theoretical basis, accepted on an empirical one, and could be treated in a manner as objectively as possible. The basis of comparison was both the clinical localization of the defect and the visual interpretation of the VEPM. It is hoped that a statistical procedure could be developed which does not require any subjective judgement.

2. Materials and Methods

The patient population consisted of 12 children (age 1 to 10 years, median 3 years). All were examined with particular emphasis on their neurological and visual systems, including visual field examination at the bedside. All 12 patients had unilateral homonymous hemianopia on clinical examination. The etiology of the field defects varied among the patients. For three of the patients we had multiple VEPMs performed at various points during the clinical recovery. These data were only used to further test the techniques analyzed.

> The problem that seemed most tractable for our study is that of symmetry, namely, whether the two sides of the brain react in a similar way to the incoming symmetric stimuli.

The control group consisted of 23 normal subjects (age 6 to 18 years, median 10.8 years) with no history of neurological disturbance or visual defect.

The subjects were not sedated and during testing laid supine in a darkened room. The strobe unit was placed 10 inches in a direct line of sight from the patient's closed eyes. Continuous effort was made to ensure alertness. Collodion electrodes were used, with impedence less than 3K Ohm. Twenty simultaneous channels (International 10–20 system, including 0_z) were available to acquire data for 512 ms after each flash stimulus. The input was led to a 21 channel electroencephalogram (Nihon Kohden Corporation model 4221, Irvine, California) and its output digitized at 500 Hz by a dedicated microcomputer (Biologic Systems Corporation model Brain Atlas, Northbrook, Illinois). Two hundred stimuli were averaged with automatic artifact rejection to form a single average evoked potential. Visual interpretation was done with prior knowledge of any identification or clinical information. The VEPM data was transferred into an ASCII file and analyzed with the methods

described below by using the Systat statistical package (Systat Inc., Evanston, Illinois).

The problem that seemed most tractable for our study is that of symmetry, namely, whether the two sides of the brain react in a similar way to the incoming symmetric stimuli. Several statistics were constructed.

2.1 Correlation Coefficients:

The Pearson correlation coefficient was computed for the data from the 8 homologous electrode pairs: F_{p1}-F_{p2}, F_3-F_4, F_7-F_8, C_3-C_4, T_3-T_4, P_3-P_4, T_5-T_6, and O_1-O_2. The control group was used to construct onesided 95% normal confidence intervals. Values below the lower limit of such interval were considered abnormal.

2.2 Multiple Correlation:

Multiple correlation coefficients were computed for each of the lateral occipital channels with respect to the adjacent channels (O_1 with respect to T_5, P_3, P_Z and O_z; O_2 with respect to P_Z, P_4, T_6 and O_7). A two sided 95% confidence interval was constructed using the normal subjects and then the values obtained for the patients were tested against such interval. If a strong local source was present near O_1, say, a high spatial gradient would exist, giving a lower correlation. Conversely, a higher correlation value would result from a low spatial gradient as a result of volume conduction from distant generators.

2.3 Mahalanobis Distance:

Each EP series of 256 points was divided into 8 time bins of 64 ms, with a single average voltage computed per bin. This produced response vectors from which the mean value and the covariance matrixes were estimated, separately for the patient and control groups. The Mahalanobis distance[3] of each response from both groups was then computed and the VEP classified to belong in the group with the smaller distance. In order to respect the independence and the meaningfulness of the data we used only the left channel (O_1) for the control subjects and the abnormal side for the patients.

2.4 Cross-correlation Analysis:

This type of analysis was limited to the O_1-O_2 pair. The correlations between O_1 and O_2, in this order, were computed at lags varying from −20 to +20 (i.e. −40 to +40 ms) and the following set of statistics was constructed for each VEP:

— the lag at which maximum correlation occurred;
— the value of the correlation at lag 0;
— the ratios of the correlation at lag 0 to those at lag −20 and +20 independently (skewness ratios).

These were all taken as non parametric statistics, as no assumptions were made about their distribution. The two ratios presented an additional problem, namely that for some EP's the correlation at one of the three lags considered was negative. In order to maintain interpretability we assigned to these ratios a value of 0 whenever the correlation at lag 0 was negative and a value of 100 whenever the correlation at lag 0 was positive but was negative at the corresponding extreme.

3. Results

Visual interpretation resulted in 11/12 (92%) VEPMs being classified as abnormal, while 1 was classified as normal.

3.1 Correlation Coefficients:

The set of correlation coefficients provided some indication of the nature of the VEP investigated. Of the 23 control subjects 13 had all correlations within the confidence limit, 7 had one abnormal value, 2 had two abnormal values and 1 had three. Of the 12 patients 1 had 1 abnormal value, 1 had them all abnormal and the remaining had between 3 and 7 abnormal values, mostly in the occipital region (see Table 1).

Table 1

Summary of statistics for correlation coefficients

				# of cases below limit	
Ch. pair	Mean	St. dev.	Lower limit	CONTROL	PATIENT
F_{p1}-F_{p2}	.975	.028	.928	2/23	5/12
F_3-F_4	.925	.088	.780	3/23	2/12
F_7-F_8	.776	.249	.366	1/23	5/12
T_3-T_4	.827	.148	.583	2/23	10/12
C_3-C_4	.923	.071	.806	1/23	6/12
P_3-P_4	.891	.100	.726	1/23	9/12
T_5-T_6	.812	.122	.611	2/23	10/12
O_1-O_2	.923	.082	.788	2/23	10/12

3.2 Multiple Correlation:

Multiple correlation produced disappointing results. The confidence interval obtained from the control group was too wide and close to unity to provide any discrimination value for the patient group (mean 0.987, S.D. 0.011, 95% interval 0.965 to 1). Of the 46 values for the control group 2 were classified as abnormal. Of the 24 values for the patient group only 5 were classified as abnormal and two of these referred to the side which, on clinical examination, had proved less abnormal.

3.3 Mahalanobis Distance:

The Mahalanobis distance method provided only one misclassification in the control group, but only 7 of the 12 patients were correctly classified as abnormal.

3.4 Cross Correlation:

Based on the values obtained from the control group we set the following *ad hoc* discrimination rule. A reading was considered abnormal if:

— the maximum correlation was at a lag lower than −5 or higher than +5 or,
— the correlation at 0 was lower than 0.6 or,
— one of the skewness ratios was lower than 1.5.

With this criterion all control subjects were classified as normal and all patients in the study group as abnormal except one (92%), the same accuracy as visual interpretation. The exception was caused by a type of abnormality not revealed by

TABLE 2

Mahalanobis distance.

Individual controls' distance from:			Individual patient's distance from:		
Control group	Patient group	Classif.	Control group	Patient group	Classif.
2.410	3.450	n	3.810	4.600	n
6.100	48.990	n	4.290	4.990	n
3.100	22.110	n	66.740	10.000	a
7.500	129.880	n	29.330	9.780	a
7.290	46.460	n	11.810	9.950	a
4.910	17.920	n	4.550	4.920	n
4.480	7.260	n	68.700	7.960	a
3.100	48.530	n	6.310	8.420	n
9.290	568.860	n	22.130	8.590	a
13.790	392.200	n	6.880	5.290	a
1.400	12.540	n	6.810	7.970	n
3.790	3.070	a	10.680	5.530	a
3.550	11.620	n			
7.590	45.470	n			
6.630	82.310	n			n = 5/12
19.870	142.760	n			
9.430	486.660	n			a = 7/12
8.700	47.060	n			
13.470	158.030	n			
15.380	172.970	n			
10.820	185.250	n			
10.920	47.130	n			
2.470	76.300	n			
		n = 22/23			
		a = 1/23			

n = individual is closer to the control group.
a = individual is closer to the patient group.

TABLE 3

Cross-correlation study

	Lag of max. correlation	Correlation at lag 0	Ratio with corr. at −20	Ratio with corr. at +20
CONTROL GROUP				
	0	0.958	2.047	2.777
	−1	0.975	1.509	1.908
	0	0.928	1.657	2.812
	0	0.976	1.852	2.509
	0	0.736	3.242	3.472
	0	0.916	5.234	1.722
	0	0.857	12.243	100.000
	0	0.874	28.194	16.491
	2	0.954	100.000	954.000
	0	0.949	100.000	100.000
	−1	0.929	1.621	2.617
	0	0.989	12.519	6.774
	0	0.972	2.467	1.873
	0	0.973	1.954	1.900
	−2	0.922	1.592	2.499
	−1	0.984	1.922	2.491
	0	0.939	1.912	1.940
	2	0.898	10.090	4.157
	0	0.961	1.806	2.164
	1	0.958	1.808	1.797
	−1	0.969	16.424	100.000
	0	0.971	1.994	2.111
	1	0.648	2.455	7.714
PATIENT GROUP				
	17 *	0.185 *	1.063 *	0.564 *
	0	0.296 *	10.963	100.000
	−20 *	0.387 *	0.531 *	1.155 *
	−10 *	0.500 *	1.018 *	100.000
	−1 *	0.928	1.291 *	1.925
	−2	0.862	1.626	1.523
	20 *	−0.248 *	0.000 *	0.000 *
	20 *	−0.190 *	0.000 *	0.000 *
	−20 *	−0.230 *	0.000 *	0.000 *
	−20 *	0.279 *	0.398 *	100.000
	−20 *	0.079 *	0.140 *	100.000
	−17 *	0.476 *	0.815 *	23.800

The asterisks indicate values beyond the set limits.

the procedure, namely the patterns of the two channels were well matched in phase, but quite different in amplitude.

4. Discussion

We were initially concerned about the age difference between the patient and control group. However we believed that the type of features under study (mainly correlations) would not be affected by age, unlike some latency values or morphological features. In fact an inspection of all the data revealed no systematic difference in the quantities analyzed between low and high age subjects.

4.1 Correlation Coefficient:

While correlation coefficients are the first choice for an analysis of this type and despite the fact that they did prove useful, some technical considerations would suggest intrinsic limitations.

First of all, for a normal subject one would expect the value of each such coefficient to be close to 1. In this case the distribution of the sample correlation, even under the usual assumptions of normality and independence of the data, tends to normality very slowly[4]. In fact it is not asymptotically normal if the true coefficient is exactly 1. This means that one may not correctly use normal confidence intervals to test individual readings. This theoretical fact was confirmed by our data: the histogram of the correlation coefficients for the control group was quite skewed and normal confidence intervals failed to create a convincing division between the two groups.

We were initially concerned about the age difference between the patient and control group.

It is perhaps worth mentioning that even if we had used a non-symptotic distribution theory for these coefficients, an "abnormal reading" would tell us very little about the nature of the abnormality, since this may be due to a phase shift, reversal, or unilateral low amplitude reading. Similarly, an abnormal result with large slow waves and missing peaks, which would present as a featureless reading of normal amplitude, may provide a high correlation coefficient, thus masking a striking abnormality together.

There is always the possibility of spurious findings on the basis of repeated or multiple statistical tests applied to the data[5]. This difficulty may be overcome by the use of a proper multiple comparison procedure[6].

4.2 Multiple Correlation:

The lack of usefulness of multiple correlation coefficients is likely caused by the great variability present in the data and by the variety of causes which may generate large values for this coefficient. This problem, which is already noticeable in the simple correlation case, became overwhelming when dealing with multiple correlations. No simple solution was found.

4.3 Mahalanobis Distance:

The method based on calculation of the Mahalanobis distance can be, in our opinion, quite effective. Several technical factors limited its use in the current study. First it requires estimation of the covariance matrix for both control and patient groups. Hence if we want to look at a fine time axis subdivision (i.e. bins of 8 ms or less) a large number of cases is needed in each group in order to obtain reasonable estimates. With the current number of cases we could only divide the total epoch into 64 ms bins and therefore some precision was lost. Short of obtaining a much larger number of VEP, one could limit attention to part of the VEP, say 80–200 ms. or chose as response variables some of the morphological features of the VEP, suitably quantified. This last option however would reintroduce the element of subjectivity that we are trying to eliminate.

Finally, it would be better to use one set of data to estimate mean vectors and covariance matrices and another to test the resulting procedure, but again this was not possible with the number of cases available.

4.4 Cross Correlation:

The analysis of cross-correlations proved very effective, despite the degree of arbitrariness that it required. It utilizes correlation coefficients in a non parametric, and so more acceptable way, and was developed based on the following considerations. In an ideal normal subject one would expect a fairly high positive correlation at lag 0, due to symmetry, and rapidly decreasing values as the two series are shifted with respect to one another, due to the richness of features of the EP. On the other hand if one side is delayed with respect to the other one would notice a maximum correlation at some lag different from 0, corresponding to the phase (latency) shift. Further, a unilaterally low amplitude result (e.g. unilateral cortical destruction) would generate low values at all lags, while a symmetric but featureless EP (which may indicate a bilateral disorder), would decrease quite slowly at either side of 0.

The choice of the value 100 for the case of negative correlation at one extreme should not cause any concern, again because we are treating these ratios non parametrically; a value of 30 is just as positive a finding as 60, not half as much.

The problem of the lack of sensitivity to amplitude asymmetries has to do with the calculation of cross-correlation. Local variations of slope (i.e. small peaks or troughs) are de-emphasized. We believe that these shortcomings may be corrected by the use of further statistics which emphasize local morphological features.

If the main occipital peak (DEF component)[7] is the dominant peak in the EP, a maximum correlation achieved at a large negative lag accompanied by a low but positive first ratio, may be a strong indication of a left side abnormality, based on a larger latency. This however requires subjective knowledge of the EP morphology.

> Our preliminary study suggests that a useful approach to the objective interpretation of a VEP is in terms of cross-correlations.

More generally, the use of all four variables considered may provide a better understanding of the nature of the asymmetry than the correlation coefficient alone.

The statistics we have considered were aimed at detecting asymmetries and none could clearly identify the abnormal side. However we believe that the Mahalanobis distance has the potential to do so, once the optimal division of the series is identified and a sufficient number of cases is available.

5. Conclusion

Our preliminary study suggests that a useful approach to the objective interpretation of a VEP is in terms of cross-correlations. In the small sample studied, this method gave the same accuracy as visual interpretation of the VEPM. The statistics we chose seemed to discriminate quite effectively between control and patient groups. Further work along these lines and a better understanding of the statistical properties of the variables involved seems worthwhile. In particular it will be crucial to validate that the set limits do in fact represent threshold values, and are not artifacts of our small set of data.

6. References

1. D.Regan: *Evoked Potentials in Psychology, Sensory Physiology and Clinical Medicine*. (Chapman and Hall, London 1972) p. 173.
2. K.A. Kooi, R.E. Marshall: *Visual Evoked Potentials in Central Disorders of the Visual System*. (Harper and Row, New York 1979) pp. 3–5.
3. D.F. Morrison: *Multivariate Statistical Methods*, 2nd ed. (McGraw-Hill, New York 1976) p. 235.
4. M.G. Kendall, A. Stuart: *Advanced Theory of Statistics*, Vol. 2, 3rd ed. (Hafner, New York 1969) p. 341.
5. B.S. Oken, K.H. Chiappa: Statistical issues concerning computerized analysis of brainwave topography. *Ann. Neurol. 19*, 493 (1986)
6. K. Godfrey: Comparing the means of several groups. *N. Engl. J. Med. 313*, 1450 (1985)
7. R.E. Dustman, E.C. Beck: The effects of maturation and aging on the wave form of visually evoked potentials. *Electroenceph. Clin. Neurophysiol. 26*, 2 (1969)