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Multivariate Spectral Methods for the Analysis of Event-Related Brain Potentials

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The purpose of this article is to present some useful mathematical models for the analysis of multiple electrode event-related brain potential (ERP) experiments. We describe a multivariate spectral method for eye-movement removal and we also describe a multivariate spectral method for the analysis of multiple lead repeated measures data. The complex T^2 and the complex Behrens–Fisher Problem are also discussed. All of the above methods are applied to experimental ERP data for four electrodes, two groups and two repeated factors. © 1988 Academic Press, Inc.

Recent research (*1–4*) on event-related brain potentials (ERPs) has begun to address questions concerning scalp distributions of ERPs collected from multiple electrodes. In most previous research on ERPs, the statistical analyses employed have considered one electrode location at a time rather than all of them simultaneously. Also, the analysis of multiple lead data has resulted in issues concerning statistical techniques (*5–7*). Statistical methods that have been used are principal components analysis, amplitude and latency analysis of defined components, and spectral analysis. Univariate methods are adequate if the intercorrelations of potentials among leads are small, whereas multivariate methods of analysis can be superior if the intercorrelations are moderate to large. In (*8*) is shown that there are many statistically significant coherences among electrodes. Likewise, in the data that we shall discuss in the present study, there are many significant coherences between leads so that good statistical performance of multivariate methods would be expected. In a previous article, Rawlings (*9*) has discussed the utility of spectral methods in multiple lead problems, and in (*10*) multivariate spectral methods were used in developing a technique for performing discriminant analyses between two clinical groups.

In the present article the analysis of multiple lead data using the complex T^2 statistic and the complex general linear model will be discussed. The methods will be illustrated with data from an ERP experiment using visual evoked potentials, and the experimental design will be of the repeated measures type.

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The analysis of the data leads to the use of a solution of the complex Behrens–Fisher problem. Also, in this article a spectral analysis method for the removal of eye-movement artifacts for multiple lead data will be presented.

Mathematical Methods

In this article we are concerned with p-dimensional time series models of the form $Y_{jl}(t) = \mu(t) + \alpha_j(t) + \varepsilon_{jl}(t)$ for two groups or $Z_l(t) = \mu(t) + \sum_{u=-\infty}^{\infty} A(t-u)x_l(u) + \varepsilon_l(t)$ for one group, where $t = 0, \ldots, T-1; j = 1, 2; l = 1, \ldots, N_j$. $\varepsilon_{jl}(t)$ and $\varepsilon_l(t)$ are zero-mean stationary Gaussian processes and $\alpha_j(t)$ and $\mu(t)$ denote the deterministic group effect and grand mean evoked potentials. It is assumed that $A(t-u)$, $x_l(t)$ satisfy the boundedness conditions discussed in Chapter 6 of Brillinger (*11*). The multivariate finite Fourier transform (FFT) of $V(t)$ is defined by $\hat{V}(k) = \frac{1}{\sqrt{T}} \sum_{t=0}^{T-1} V(t)e^{-i\lambda_k t}$, where $\lambda_k = 2\pi k/T$ for $k = 0, \ldots, T-1$. When the FFT is applied to the above time series models, we obtain $\hat{Y}_j(k) = \hat{\mu}(k) + \hat{\alpha}_j(k) + \hat{\varepsilon}_{jl}(k)$ and $\hat{Z}_l(k) = \hat{\mu}(k) + \hat{A}(k)\hat{x}_l(k) + \hat{\varepsilon}_l(k)$. From Hannan (*12*), it is known that $\hat{\varepsilon}_{jl}(k)$ and $\hat{\varepsilon}_l(k)$ have multivariate complex normal distributions, and for large T the vectors are independent for $k \neq k'$. Hence, the above time series models can be analyzed with the complex multivariate general linear model (GLM) described next.

A. Complex Multivariate GLM

The following results are derived in Khatri (*13*): Let S be a $p \times n$ complex matrix of n independent p-variate observations. The density function for S is a complex normal (*14*) CN(Z; μM, Σ), where Σ is $p \times p$, μ is $p \times q$ unknown complex, M is $q \times n$ given complex matrix of rank $q \leq n$, and Z is $p \times n$. The maximum likelihood estimates of μ and Σ are given by $\beta = Z\overline{M}'(M\overline{M}')^{-1}$ and $\psi = n^{-1}Z[I - \overline{M}'(M\overline{M}')^{-1}M]\overline{Z}'$, where $\overline{M}'$ denotes the complex conjugate transpose of M. Define $\mu = (\mu_1 \mu_2)$, $\overline{M}' = (\overline{M}_1 \overline{M}_2')$, $A = M\overline{M}' = \begin{pmatrix} A_{11} & A_{12} \\ \overline{A}_{12}' & A_{22} \end{pmatrix}$, where μ_1 is $p \times q_1$, μ_2 is $p \times q_2$, $q_2 = q - q_1$, M_1 is $q_1 \times n$, M_2 is $q_2 \times n$, A_{11} is $q_1 \times q_1$, A_{12} is $q_1 \times q_2$, and A_{22} is $q_2 \times q_2$.

Consider the test of the hypothesis H_0: $\mu_1 = 0$ versus the alternative H_1: $\mu_1 \neq 0$. The likelihood ratio test is performed with the statistic $\Lambda_1 = |\psi|/|\psi + n^{-1}\beta_{1.0}A_{11.2}\overline{\beta}_{1.0}'|$, where $A_{11.2} = A_{11} - A_{12}A_{22}^{-1}\overline{A}_{12}'$, $\beta_{2.0} = Z\overline{M}_2'A_{22}^{-1}$, and $\beta_{1.0} = (Z\overline{M}_1' - \beta_{2.0}\overline{A}_{12}')A_{11.2}^{-1}$. The distribution for $-m \ln \Lambda_1$ is given by $\Pr(-m \ln \Lambda_1 \leq \zeta) \cong \Pr(\chi_f^2 \leq \zeta) + r_2 m^{-2}[\Pr(\chi_{f+4}^2 \leq \zeta) - \Pr(\chi_f^2 \leq \zeta)] + 0(m^{-3})$, where $m = 2n + q_1 - p$, $f = 2pq_1$, and $r_2 = pq_1[p^2 + q_1^2 - 2]/3$.

Let C denote a $s \times p$ matrix of contrast row vectors, and the hypothesis $\nu_1 = C\mu_1 = 0$ is to be tested. This can be accomplished as follows: First create the s-dimensional variables Cz_i, $i = 1, \ldots, n$ from the p-dimensional observation vectors z_i. Next, test the hypothesis $\nu_1 = 0$ by using the new observation vectors in the complex GLM with p replaced by s. This procedure will be useful when performing repeated measures tests later.

B. Complex T^2

The following results are derived in Giri (*15*):

Let η be a complex Gaussian random p-variate vector such that $E(\eta) = \alpha$ and $\Sigma = E(\eta - \alpha)(\eta - \alpha)^*$ is the complex covariance matrix, where $*$ denotes the complex conjugate transpose. The maximum likelihood estimates $\hat{\alpha}$ and $\hat{\Sigma}$ are given by $N\hat{\alpha} = \sum_{i=1}^{N} \eta_i = N\overline{\eta}$ and $N\hat{\Sigma} = \sum_{i=1}^{N} (\eta_i - \overline{\eta})(\eta_i - \overline{\eta})^* = A$, where N is the number of independent, identically distributed p-variate complex Gaussian random variables. Then under the null hypothesis H_0: $\alpha = 0$

$$\frac{2(N - P)}{2P} T_c^2 = F_{2P,2(N-P)},$$

where $T_c^2 = N\overline{\eta}^* A^{-1}\overline{\eta}$.

C. Behrens–Fisher Problem

Consider the problem of testing for the mean differences among groups. If the covariance matrices for the groups are not equal, then the problem is called the Behrens–Fisher problem. One solution for this problem is presented in Eaton (*16*) for real variables, and this solution also generalizes to the complex variable case. Only the simple case of two groups with equal numbers of observations will be discussed.

Let x_{ij}; $i = 1, 2$; $j = 1, \ldots, N$ denote the jth random p-dimensional observation vector from group i, where x_{ij} derives from a p-variate complex normal distribution. Now, create the new observation vectors $y_j = x_{1j} - x_{2j}$ for matched subjects. Performing the complex T^2 test on the y_j results in a test for equal means even when the group covariance matrices are unequal. This particular statistical solution of the Behrens–Fisher problem will be referred to as the Scheffe method.

Experimental Design

We have designed a P300 (*17*) study involving an experimental ($N = 25$) and a control group ($N = 25$) in the visual modality, with task difficulty determined by the complexity of processing equally physically deviant stimuli. Subjects were seated in a sound-attenuated chamber facing a computer-controlled display (CRT), with head resting on an adjustable chin rest. Subject was told to look at a fixation point displayed in the center of the screen. The experimental design consisted of a visual head orientation task. The nontarget stimulus was a frequently occurring circle presented in the center of the CRT, to which the subject did not respond. The target stimulus was an aerial view of the head with the nose and only one ear drawn in, on either the left or the right side; the subject pressed the corresponding button indicating whether a right or left ear was present as quickly as possible (reaction time). Under the "easy" condition, the head was facing forward (nose up on screen), and the left or right ear appeared directly on the side corresponding to the appropriate button. Under the "difficult" condition, the head was facing back (nose down on screen), and either the left or the right ear appeared on the opposite side of the screen to the corresponding button. A total of 240 stimuli were randomly presented—160 nontargets and 80 target (20/target condition). The stimuli were 25 msec in duration and subtended 2.9 degrees of arc; interstimulus intervals varied randomly between 2 and 4 sec.

Monopolar ERPs were recorded from midline frontal (F_z), central (C_z), parietal (P_z), and occipital (O_z) scalp leads. The linked ears served as reference and the nasion served as ground. Eye movements were recorded by electrodes placed above and below the right eye. ERPs were sampled (142 points/sec; bandwidth 0.01–100 Hz) by a PDP 11/40 computer for 49 msec preceding the stimulus (baseline) and for 700 msec following the stimulus. The prestimulus baseline voltage level was subtracted from each ERP recording at each electrode. Trials with excessive eye-movement contamination (50 μV or more) were automatically discarded. The experiment continued until a total of 20 artifact-free responses were obtained for each target and nontarget.

Multivariate Eye-Movement Removal

We now present a multivariate method for the removal of eye-movement artifacts. This method is a generalization to multiple leads of the univariate technique employed in (*18*). Any additional eye-movement contamination from a subject can be removed by using the complex GLM (the second model under Mathematical Methods) at each frequency λ_k. In our case

$$n = 20,\ p = 4,\ q_1 = 1,\ q_2 = 1,\ \mu = \begin{vmatrix} \mu_1 & b_1 \\ \mu_2 & b_2 \\ \mu_3 & b_3 \\ \mu_4 & b_4 \end{vmatrix} = [\mu_0 \quad b_0],$$

where the first column corresponds to the four intercepts and the last column corresponds to the four regression coefficients with the EOG lead. Also $M = \begin{bmatrix} 1 & \cdots & 1 \\ z_{1,1} & \cdots & z_{1,20} \end{bmatrix}$, where $z_{1,l}$ denotes the lth observed EOG value at λ_k. The result of the test of Λ_1 is a test of the hypothesis $\mu_0 = 0$. μ_0 corresponds to zero input from the EOG lead. The estimate of μ_0, $\hat{\mu}_0$, at each frequency λ_k, $k = 0, \ldots, T - 1$, was obtained and the likelihood ratio test using Λ_1 at each frequency was performed. The $4 \times T$ dimensional matrix Q was constructed in

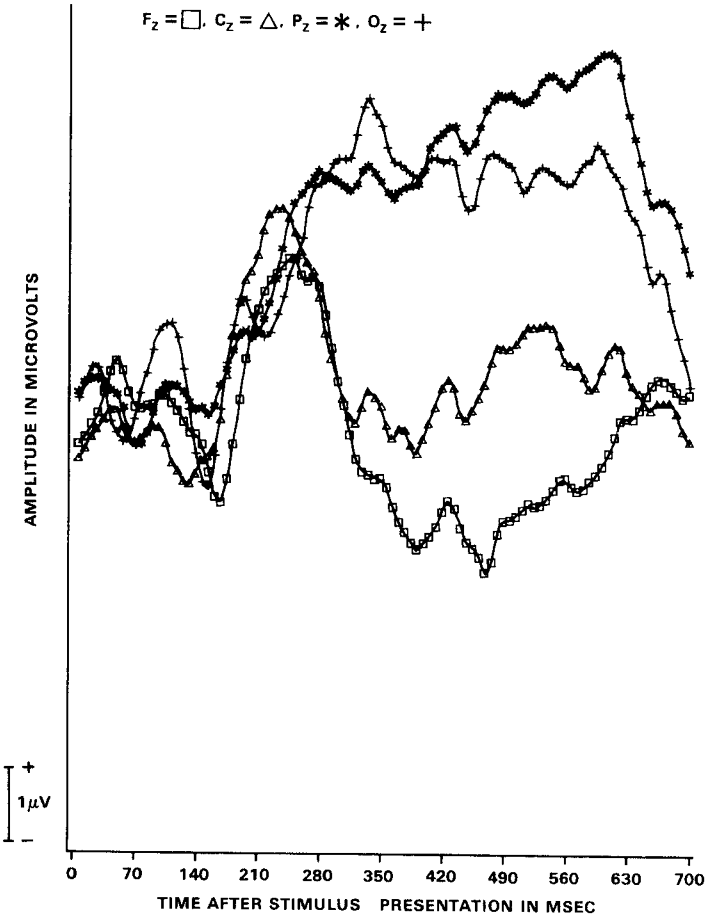

FIG. 1. Estimated event-related potentials, unadjusted for eye movement, recorded for a single subject from midline frontal, central, parietal, and occipital locations.

the following manner: If the test of Λ_1 is significant at λ_k then retain $\hat{\mu}_0$ as the $(k + 1)$th column vector of Q. Otherwise, set the $(k + 1)$th column vector of Q to zero. After completing the construction of Q an inverse FFT was performed for each row of Q. The result will be the four ERP estimates adjusted for eye movement for that subject. In Figs. 1 and 2 the unadjusted and adjusted ERP estimates for four leads for the hard-left stimulus are presented for one subject.

COMPLEX REPEATED MEASURES

The complex GLM (the first model under Mathematical Methods) can be used for the analysis of multivariate repeated measures tests. A comprehensive

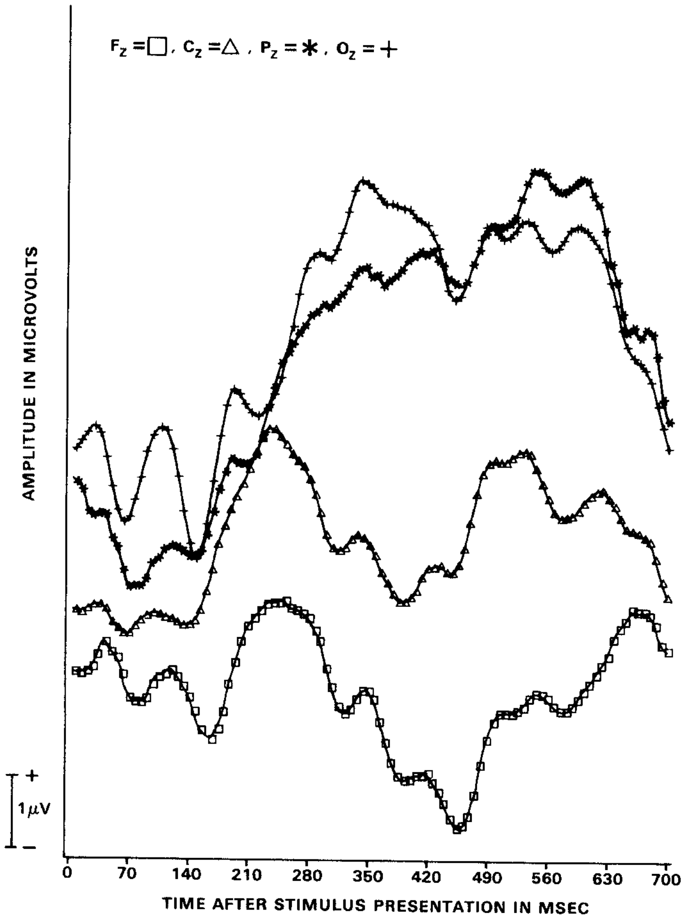

FIG. 2. Estimated event-related potentials, adjusted for eye movement, recorded for a single subject from midline frontal, central, parietal, and occipital locations.

discussion of these types of tests in the real variable case is contained in Timm (*19*).

The four electrode problem of two groups (G) and two repeated measures factors, easy–hard (EH) and left–right (LR), are considered. Define y_{jl} and $\nu_j = E(y_{jl})$, where

$$y_{jl} = (y^{jl}_{11}y^{jl}_{12}y^{jl}_{13}y^{jl}_{14}y^{jl}_{21}y^{jl}_{22}y^{jl}_{23}y^{jl}_{24}y^{jl}_{31}y^{jl}_{32}y^{jl}_{33}y^{jl}_{34}y^{jl}_{41}y^{jl}_{42}y^{jl}_{43}y^{jl}_{44})'$$

$$\nu_j = (\nu^{j}_{11}\nu^{j}_{12}\nu^{j}_{13}\nu^{j}_{14}\nu^{j}_{21}\nu^{j}_{22}\nu^{j}_{23}\nu^{j}_{24}\nu^{j}_{31}\nu^{j}_{32}\nu^{j}_{33}\nu^{j}_{34}\nu^{j}_{41}\nu^{j}_{42}\nu^{j}_{43}\nu^{j}_{44})'.$$

The second lower index designates the electrode, and the first lower index designates the cell of the factorial design in the following sequence: easy–left, hard–left, easy–right, hard–right. In terms of the GLM we have $p = 16$, $q = 2$, $q_1 = 1$,

$$\mu = \begin{pmatrix} \alpha_{11}\alpha_{12}\alpha_{13}\alpha_{14}\alpha_{21}\alpha_{22}\alpha_{23}\alpha_{24}\alpha_{31}\alpha_{32}\alpha_{33}\alpha_{34}\alpha_{41}\alpha_{42}\alpha_{43}\alpha_{44} \\ \mu_{11}\mu_{12}\mu_{13}\mu_{14}\mu_{21}\mu_{22}\mu_{23}\mu_{24}\mu_{31}\mu_{32}\mu_{33}\mu_{34}\mu_{41}\mu_{42}\mu_{43}\mu_{44} \end{pmatrix}',$$

where the parameters μ_{ij} denote the grand mean and the α_{ij} denote the group effect in the reduced model. In our case $n = 50$ since there are 25 observations in each group. $M = \begin{pmatrix} 1 & \cdots & 1 & -1 & \cdots & -1 \\ 1 & \cdots & 1 & 1 & \cdots & 1 \end{pmatrix}$, where the top row contains 25 ones and 25 negative ones while the bottom row contains 50 ones. The test of the hypothesis $\mu_1 = 0$ in the above model is a test for group differences on any of the 16 variables. In all of the tests discussed below, the contrast matrix C is presented which is used to test the appropriate hypothesis.

(*a*) *LR × EH × G interaction.*

$$C = \begin{pmatrix} 1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 1 \end{pmatrix} = (I_4 \vdots -I_4 \vdots -I_4 \vdots I_4).$$

(*b*) *LR × G interaction.*

$$C = (I_4 \vdots I_4 \vdots -I_4 \vdots -I_4).$$

(*c*) *EH × G interaction.*

$$C = (I_4 \vdots -I_4 \vdots I_4 \vdots -I_4).$$

(*d*) *Group effect.*

$$C = (I_4 \vdots I_4 \vdots I_4 \vdots I_4).$$

In order to test the within-groups effects one must first modify M by interchanging the rows of M. Then the GLM test for $\mu_1 = 0$ will correspond to a grand mean test for all 16 variables.

(*e*) *EH effect.*

$$C = (I_4 \vdots -I_4 \vdots I_4 \vdots -I_4).$$

(*f*) *LR effect.*

$$C = (I_4 \vdots I_4 \vdots -I_4 \vdots -I_4).$$

(*g*) *EH × LR interaction.*

$$C = (I_4 \vdots -I_4 \vdots -I_4 \vdots I_4).$$

One of the assumptions of the GLM model is that the complex covariance matrices are equal. A test for the equality of spectral matrices is described in Rawlings *et al.* (*10*), and this test was used on the observation vectors of 16 variables. Except at frequency 0 the test was significant at the level 0.0005 or better. Hence, rather than proceeding with above tests, the within-groups tests for one group at a time are considered. The tests described below are performed by using the complex T^2 test on the observation vectors $Cy_{jl}; j = 1, 2; l = 1, \ldots, 25$, where C is the appropriate matrix of contrast vectors.

(*h*) *EH effect.*

$$C = (I_4 \vdots -I_4 \vdots I_4 \vdots -I_4).$$

(*i*) *LR effect.*

$$C = (I_4 \vdots I_4 \vdots -I_4 \vdots -I_4).$$

(*j*) *EH* × *LR effect.*

$$C = (I_4 \vdots -I_4 \vdots -I_4 \vdots I_4).$$

In order to perform the between-groups tests, the Scheffe method was used on the observation vectors $Cy_{jl}; j = 1, 2; l = 1, \ldots, 25$, where C is the appropriate matrix of contrast vectors.

(*k*) *LR* × *EH* × *G effect.*

$$C = (I_4 \vdots -I_4 \vdots -I_4 \vdots I_4).$$

(*l*) *LR* × *G effect.*

$$C = (I_4 \vdots I_4 \vdots -I_4 \vdots -I_4).$$

(*m*) *EH* × *G effect.*

$$C = (I_4 \vdots -I_4 \vdots I_4 \vdots -I_4).$$

(*n*) *Group effect, G.*

$$C = (I_4 \vdots I_4 \vdots I_4 \vdots I_4).$$

(*o*) *Easy group effect,* G_E.

$$C = (I_4 \vdots \mathrm{O} \vdots I_4 \vdots \mathrm{O}).$$

(*p*) *Hard group effect,* G_H.

$$C = (\mathrm{O} \vdots I_4 \vdots \mathrm{O} \vdots I_4).$$

RESULTS

The results of the above tests are presented in Table 1 for probability levels 0.05, 0.01, and 0.005. Since there are so many tests performed, it would be advisable to use 0.005 levels or better to avoid spurious significant results. It is then observed that there are no significant matched groups effects, but there

TABLE 1

SIGNIFICANT (*0.05, **0.01, ***0.005) RESULTS FOR SINGLE GROUP AND MATCHED GROUP TESTS FOR THE FOUR LEAD (F_z, C_z, P_z, O_z) PROBLEM

HZ	G1 EHXLR	G2 EHXLR	G1 LR	G2 LR	G1 EH	G2 EH	G	LRXG	EHXG	LRXEHXG	G_H	G_E
0.0					*							
1.43					**							
2.86	*				***							
4.29					*							
5.71												
7.14												
8.57												
10.00					***							
11.43												
12.86												
14.29												
15.71	*				*							
17.14												
18.57			*									
20.00												
21.43												
22.86												
24.29					**							
25.71												
27.14				*								
28.57			*				*					**
30.00												
31.43						*						
32.86												
34.29	*								**			
35.71												
37.14									*			
38.57	*									*		
40.00												
41.43												
42.86												
44.29							**				*	
45.71												
47.14												
48.57						***			*			
50.00									*			
51.43					*							
52.86							*					*
54.29												**
55.71										*		
57.14												
58.57												*
60.00												
61.43												
62.86									*			*
64.29												
65.71												*
67.14												
68.57									*			
70.00												
71.43												

are two significant single group effects. For group 1 (experimental) the significant EH effects are at low frequencies, 2.86 and 10.00 Hz. For group 2 (controls) the significant EH effect is at the high frequency 48.57 Hz.

Since the sample size (N = 25) is not very large for the problem of four electrodes one should be concerned about the power of the tests. In Table 2 the results for the above tests are presented for the two lead problem, P_z and O_z. It can be seen that there are several more significant results than for the four lead problem. There is a significant matched group effect, EH × G effect, G_E effect,

TABLE 2

SIGNIFICANT (*0.05, **0.01, ***0.005) RESULTS FOR SINGLE GROUP AND MATCHED GROUP TESTS FOR THE TWO LEAD (P_z, O_z) PROBLEM

HZ	G1 EHXLR	G2 EHXLR	G1 LR	G2 LR	G1 EH	G2 EH	G	LRXG	EHXG	LRXEHXG	G_H	G_E
0.0												
1.43					***		*				*	*
2.86					***							
4.29												
5.71												
7.14				*								
8.57						*						
10.00					***							
11.43					*	*						
12.86					*							
14.29												
15.71							*				*	
17.14	*											
18.57												
20.00					*							
21.43												
22.86												
24.29	*				***							
25.71												
27.14					*							*
28.57			*				***					***
30.00												
31.43	*											
32.86				*								
34.29	***				*				***	*		
35.71										*		
37.14			*		*				*			
38.57	*				*					***		
40.00												
41.43												
42.86												
44.29						*	*		*		*	
45.71												
47.14			*		*			*				
48.57					*	*			**			
50.00			*		*		*		**			*
51.43					***				**			*
52.86							*					
54.29					*				*			**
55.71	*									*		**
57.14					*				*			
58.57			*		*				*			
60.00									*			
61.43						*						
62.86	**								*	*		*
64.29					*							*
65.71	*											*
67.14					*				*			*
68.57	*				*				*	*		*
70.00	**				*				*			
71.43	*											

and LR × EH × G effect. For group 2 there are no significant effects while for group 1 there are significant EH × LR effects and EH effects. Hence, one would expect to find several more significant results for the four lead problem if a larger sample size were available.

The above results suggest that the two groups differ with group 2 having a smaller number of significant effects than group 1. The easy–hard factor appears to be the major significant factor for group 1. The left–right factor does not appear to differ between the groups.

Conclusions

In this article we have demonstrated methods for eye-movement removal and analysis of repeated measures ERP experiments for multiple leads. For the study of group differences when there are large spectral matrix differences (as in our data) then the complex T^2 and Scheffe's method can be used. Using results from a typical four lead experiment we have shown the utility of the mathematical methods described. However, the results from a two electrode model suggest that we might find even more significant effects in the four lead model if we had a larger sample size. If the above methods are to be used for large numbers of leads then it appears that larger sample sizes will be necessary for the groups.

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