Auditory Recovery Function and P3 in Boys at High Risk for Alcoholism[1]

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BEGLEITER, H., B. PORJESZ, R. RAWLINGS AND M. ECKARDT. *Auditory recovery function and P3 in boys at high risk for alcoholism.* ALCOHOL 4(4) 315–321, 1987.—We have previously reported P3 decrements in boys at risk for alcoholism in a complex visual rotation reaction time task. The present study investigated the generalizability of these observations by studying a new high risk sample of boys of Type 2 alcoholic fathers under different experimental conditions. The current experimental design consisted of an easy auditory oddball task (P3) which stressed accuracy over speed of responding, and which also included variable interstimulus intervals (0.5, 1.0 and 5.0 sec), allowing recovery functions to be derived from the evoked responses to frequent non-target stimuli. The results did not yield statistically significant differences between groups in the recovery function data. However the baseline-to-peak results to the target stimulus indicated significant decreases in both P2 and P3 amplitudes in the high risk boys. No differences in latency were obtained between groups. Furthermore frequency analysis of responses to the target stimulus using a multivariate time series model indicated between-group differences at 4 frequencies (1.43, 7.14, 8.6 and 11.43 Hz). These results replicate our previous findings of P3 decrements in boys at risk for alcoholism in a new sample of sons of Type 2 alcoholics. As we have now made these observations with different experimental conditions and sensory modalities, it is suggested that these findings are generalizable.

High risk   Alcoholism   Event-related   Potentials   Neurophysiology

IN the last decade it has become more evident that genetic factors contribute to the risk of developing alcoholism. Sons of alcoholic fathers represent a special group at high risk for developing alcoholism even when they are separated from their biological parents soon after birth [12,14]. Studies of male adoptees indicate that the biological rather than the adoptive parent is predictive of later drinking problems [6–8, 13, 14]. Further evidence for a genetic predisposition comes from twin studies indicating that the concordance rate for alcohol abuse among identical twins is almost double the rate for fraternal twins [15]. The identification of a suitable biological marker that is genetically transmitted would be of value in identifying individuals before the onset of the disease. Moreover, biological markers may provide fundamental data on the etiology of alcoholism. The search for such a marker must of necessity focus on a biological variable known to be genetically determined and prevalent in abstinent alcoholics.

For the past several years in our laboratory we have used a variety of evoked potential (EP) techniques to assess possible brain dysfunction in abstinent alcoholics. We have observed deficits ranging from abnormal conduction velocity of the wave III–V complex of the auditory brain stem poten-

tial [14] to a significant reduction in the amplitude of the P3 component of the event-related potential (ERP) [19–22]. More recently, we have undertaken the study of neurophysiological activity in sons of alcoholic fathers using measures identical to those we have been examining in abstinent adult alcoholics. In one study, we recorded auditory brain stem potentials in a group of young boys at high risk for alcoholism and a matched control group. We found no statistically significant difference in the various peak latencies or interpeak latencies [3]. This observation in young boys at risk for alcoholism is in contrast to the significant latency delays of the auditory brain stem potential which have been reported in abstinent alcoholics [4,9].

We also investigated the P3 component of the event-related potential (ERP) in young boys at high risk for alcoholism and matched controls [5]. We designed a reaction-time (RT) paradigm in which the correct identification of the targets required the mental rotation of visual stimuli (aerial view of a head). This visuo-spatial task was specifically designed to assess the integrity of the non-dominant (right) hemisphere which has been reported to be deficient in abstinent alcoholics. Moreover, we had already collected electrophysiological data with this task in abstinent alcoholics

which yielded significant ERP differences between alcoholic patients and controls [2].

Our data from this visual mental rotation task indicate that there are significant P3 amplitude differences between high risk and low risk subjects similar to those obtained between alcoholic patients and controls. A recent study by O'Connor *et al.* [18] used the identical visual paradigm and replicated and extended our findings to an older group of adolescent males at high risk for alcoholism.

The P3 amplitude differences obtained between high and low risk individuals were derived from voltage measurements as well as the use of basis functions (Principal Component Analysis—PCA) in the time domain. In addition we have utilized basis functions in the frequency domain. We constructed linear and quadratic discriminant functions in the spectral domain using a stepwise frequency selection procedure [23]. The best non-error rate for the four midline electrodes was obtained with the quadratic discriminant function, which enabled us to discriminate between the two groups of subjects.

In an effort to assess the generalizability of our observations, we have designed an experiment with different sensory and task variables. In the present study, we used two easily discriminable auditory tones, one occurring frequently while the other was presented infrequently. Moreover, the subjects were asked to press a button to the infrequent tone, stressing accuracy over speed.

METHOD

Twenty-three sons of alcoholic fathers between the ages of 7 and 15 with a mean age of 13.1 (S.D. 1.6) were tested. In each case the father had received an exclusive diagnosis of alcoholism (DSM III criteria) and had at one time or another been in treatment for alcoholism. The father had been hospitalized for alcoholism on several occasions and had manifested a high rate of recidivism starting with alcohol abuse during the teenage years. Moreover, the fathers manifested a high incidence of antisocial experiences such as fighting, arrests, traffic violations, etc. As a result, the high risk boys were all offspring of male alcoholics who are characterized as Type 2 (male limited) alcoholics [10].

We excluded boys whose mothers were alcoholics or who had ingested alcohol during pregnancy or drank excessively after giving birth. Only boys without medical problems and without exposure to alcohol or other substances of abuse were included in the study.

The 23 low risk (LR) subjects were boys who were matched for socioeconomic status, education and age to the high risk (HR) boys. The LR group had a mean age of 12.9 (S.D. 1.2) and did not differ significantly in age from the HR group. The LR subjects were included if they had no exposure to alcohol or other substances of abuse, and had no history of alcoholism, or other psychiatric disorder in first- or second-degree relatives. Except for alcoholism history, the same exclusion criteria were used as for the HR group.

Subjects were seated in a sound attenuated chamber and were told to look at a fixation point. We used a relatively standard procedure to study the auditory recovery function. In this procedure the amplitude of the N1 and P2 components of the auditory evoked potential vary as function of the interstimulus interval (ISI), the longer the ISI, the larger the amplitudes.

The specific paradigm consisted of the random binaural

FREQUENT (80%)-1500Hz INFREQUENT (20%)-750Hz INTER STIMULUS INTERVAL (ISI)
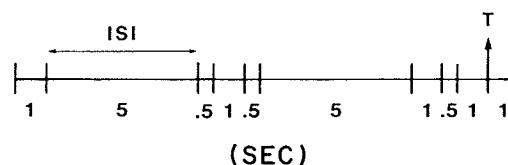

FIG. 1. Illustration of experimental paradigm. Frequent high-pitched tones (1500 Hz) occurred 80% of the time and varied in terms of the interstimulus interval (ISI) preceeding them, namely: 0.5, 1.0 or 5.0 sec. Interspersed among these frequent high-pitched tones were rare (20%) low tones (750 Hz) to which the subject responded in an auditory oddball signal detection task stressing accuracy over speed.

presentation of a high-pitched tone pip (1500 Hz; 5 msec fall and rise times) separated by 0.5, 1.0 and 5.0 second intervals (Fig. 1). The tones (40 msec duration) were presented through TDH headphones by means of a Grass click-tone control module (70 dB). Evoked potentials were averaged to these high tones according to the ISI preceding them (0.5, 1.0 and 5.0 sec) for 80 msec prestimulus and 400 msec following the tone (sampling rate 250 points/sec; bandwidth 0.1–30 Hz). Interspersed among these frequent high tones (80%) were rare low-pitched tones (750 Hz), to which the subject was asked to press a button (Fig. 1). The instructions to the subject emphasized accuracy over speed. This particular task insures a relatively high level of alertness to all stimuli. ERPs were averaged to the rare target stimuli (20%) for 140 msec preceding and 700 msec following the stimulus (sampling rate 142.85 points/sec; bandwidth 0.1–30 Hz). Responses to high-pitched tones immediately following targets (low-pitched tones) were discarded and not included in the averages of the auditory recovery function. Furthermore, trials with excessive eye-movement contamination (50 μV or more) were automatically discarded. The experiment continued until a total of 30 artifact-free responses were obtained for each ISI and rare target condition.

Monopolar evoked potentials were recorded from electrodes placed on the midline at frontal (Fz), central (Cz), parietal (Pz) and occipital (Oz) according to the 10–20 International System. The linked ears served as reference and the nasion as ground. Eye movements were recorded by electrodes placed above and below the right eye.

The baseline to peak amplitudes and latencies of the P1, N1 and P2 components were measured for the frequent stimuli at each of the three ISIs. In addition, the baseline to peak amplitudes and latencies of the P1, N1, P2, N2 and P3 components were measured to the infrequent stimulus (target). The amplitudes and latencies of the ERP components for the recovery function were subjected to a 2 (groups) $\times$ 3 (ISI) $\times$ 4 (electrodes) analysis of variance with repeated measures with Greenhouse Geisser probability levels. Similarly, ERP measures obtained to the target stimulus were subjected to a 2 (groups) $\times$ 4 (electrodes) analyses of variance with repeated measures (Greenhouse Geisser probability levels). The repeated measure ANOVA design was selected for heuristic reasons.
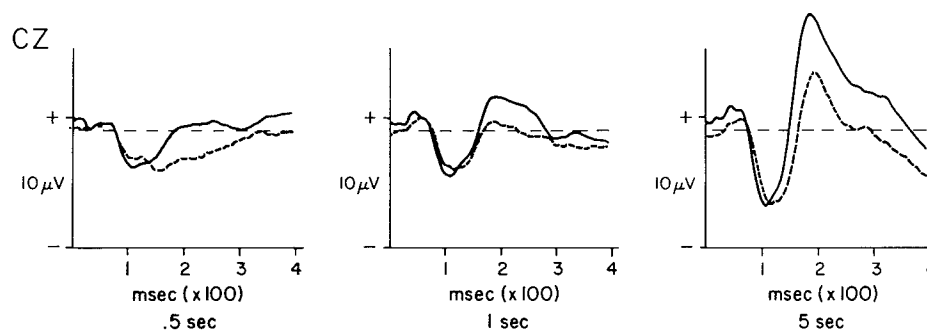
FIG. 2. Grand mean waveforms to the frequent non-target stimulus recorded at the Cz electrode according to the ISIs (0.5, 1.0 or 5.0 sec) in the HR (dashed line) and LR (solid line) subjects. Notice the differences in P_2 amplitude and recovery function between the two groups of subjects.
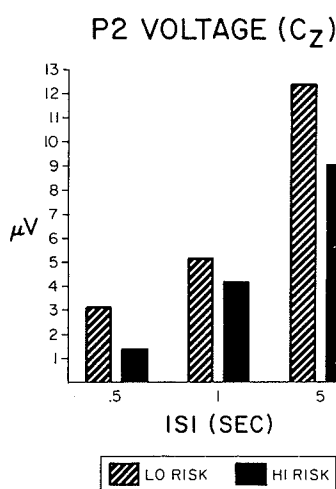

FIG. 3. Mean P2 voltage obtained to the frequent non-target tones at the Cz electrode for the short (0.5 sec), medium (1.0 sec) and long (5.0 sec) ISI in the HR and LR subjects.

TABLE 1

REPEATED MEASURES ANOVA FOR RECOVERY FUNCTION COMPONENTS

	P1 Voltage	N1 Voltage	P2 Voltage
Group (G)	0.29	0.82	1.71
ISI (I)	0.73	7.05‡	33.83‡
I × G	1.12	0.34	0.40
Electrodes (E)	0.94	43.14‡	41.84‡
E × G	1.23	1.35	3.01*
I × E	3.33‡	7.19‡	14.60‡
I × E × G	1.95	1.69	2.04

Greenhouse-Geisser Probability.
*$p<0.05$; †$p<0.01$; ‡$p<0.001$.

In addition to the aforementioned analyses of the ERP data in the time domain, we compared the frequency characteristics of the target ERPs obtained from the 23 sons of alcoholics and 23 matched controls. All baseline corrected data obtained at Pz for all target stimuli were converted to the frequency domain using a multivariate time series model [23].

RESULTS

The grand mean waveforms for the nontarget stimulus at increasing ISIs (0.5, 1.0 and 5.0 sec) are illustrated in Fig. 2. None of the statistical tests of the recovery function data yielded significant differences between high and low risk boys. It should be noted that the ANOVA comparing P2 amplitudes between high and low risk subjects at Cz approached statistical significance, $F(1,44)=3.52, p=0.06$ (Fig. 3). The recovery function paradigm was effective as indicated by significant ISI findings for N1 ($F=7.05, p<0.001$) and P2 ($F=33.83, p<0.001$) amplitudes (Table 1). None of the component latency (P1, N1, P2) comparisons was statistically significant.

The grand mean ERP waveform recorded at Pz to the target stimulus for the two groups of subjects are illustrated in Fig. 4. Statistical comparisons of the various component (P1, N1, P2, N2, P3) amplitudes for the target stimuli are shown on Table 2. The amplitude of P2 was significantly different between the HR and LR groups, $F(1,44)=13.88$, $p<0.0006$ (Fig. 5). The amplitude of the P3 component was also significantly lower for the HR than the LR groups, $F(1,44)=31.80, p<0.0001$ (Fig. 6). None of the other amplitudes were significantly different between groups. None of the latency comparisons across groups was found to be. statistically significant.

Baseline corrected data obtained at Pz for targets were converted to the frequency domain using a multivariate time series model [23]. The two groups were found to have unequal spectral matrices at the following frequencies using the likelihood ratio tests described by Shumway [25] and Rawlings et al. [23]: 5.7, 7.1, 8.6, 10.0, 11.4, 14.3, 18.6, 21.4, 24.3, 25.7, 27.1, 28.6 and 30 Hz. These results suggest that in addition to any ERP signal differences between the two groups, the two groups also manifested differences in EEG.

The finding of unequal spectral matrices necessitated the

TABLE 2

REPEATED MEASURES ANOVA FOR TARGET COMPONENTS

| | Amplitude | | | | |
	P1	N1	P2	N2	P3
Group (G)	2.64	0.05	13.88‡	2.66	31.88‡
Electrode (E)	0.77	14.83‡	38.59‡	32.36‡	50.36‡
E × G	0.71	2.01	1.86	1.40	2.02

Greenhouse-Geisser Probability.
*$p<0.05$; †$p<0.01$; ‡$p<0.001$.

use of the Behrens-Fisher statistic [1] to test for between-group mean differences in the 21 frequencies evaluated up to 30 Hz. Significant differences at the Pz electrode were obtained at the following frequencies: 1.43 ($p<0.0001$), 7.14 ($p<0.02$), 8.6 ($p<0.003$) 11.43 ($p<0.05$). Figure 7 shows these mean differences plotted in the time domain using all frequencies and using only those frequencies found to be significantly different (1.4, 7.1, 8.6 and 11.4 Hz). Visual inspection of this figure suggests that these frequency differences correspond to voltage differences primarily at 120 and 335 msec, with the at-risk boys exhibiting less negative voltage of the N1 component (around 120 msec) and less positive voltages of the P2 (around 200 msec) and P3 components (around 335 msec) than the controls.

Each of the two groups was then evaluated separately. Boys at high risk exhibited 13 frequencies significantly different from zero, while boys of non-alcoholics had 10 frequencies significantly different from zero (Table 3). Table 3 also lists the magnitude and phase spectra for those data for each group of subjects separately.

Changes at Pz in response to repeated target stimuli were evaluated by comparing the first 5 and last 5 presentations using the Behrens-Fisher statistic. The boys of alcoholic fathers showed a statistically significant change ($p<0.05$) at 4.3 Hz, whereas the control boys showed changes at 4.3 and 5.7 Hz. Moreover, direct comparisons between the two groups revealed that they differed in how they changed over presentation, with a significant difference at 25.7 Hz. The boys at high risk changed one-half the magnitude of the controls.

The observations that boys at high risk for alcoholism differed in spectral matrices of ERP from control subjects suggest that these particular variables may be of utility in classifying children at high risk. Linear and quadratic discriminant analyses were performed to determine whether boys at risk could be differentiated from controls. Prior probabilities were arbitrarily set at 0.5. A cross-validation procedure was used in which one person was left out at a time in order to estimate the accuracy of the classification procedure (Jackknife Method).

In Table 4, we present the results for the linear and quadratic discriminant analyses. In order to arrive at each entry in Table 4 for the linear analysis, we obtained a test of equal means, a test for equal spectral matrices, and a test for equal populations for each frequency [23]. Using the selected frequencies, the leaving-one-out non-error rates were determined at each step of a forward stepping procedure. By observing the number of variables at which the leaving-one-out estimates began to deteriorate, a decision was made as to the number of frequencies to include. The same frequencies
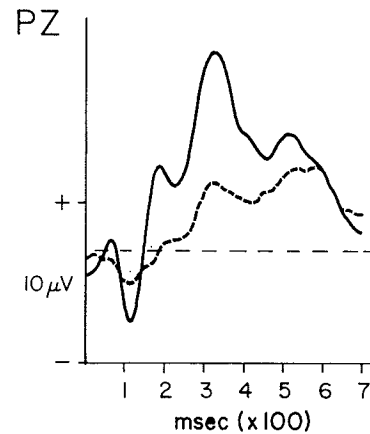

FIG. 4. Grand mean ERP waveforms recorded at Pz to the target stimulus in the low risk (solid line) and the high risk (dashed line) groups.
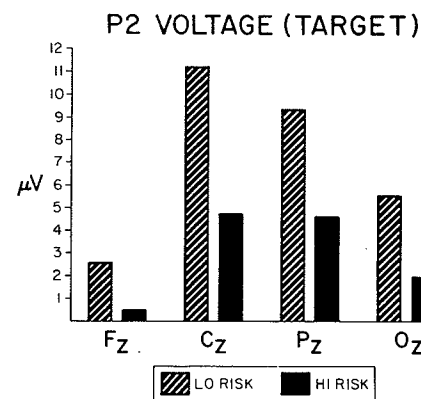

FIG. 5. Mean P2 voltage obtained to the rare target stimulus for the HR and LR groups of subjects at the four midline electrodes.
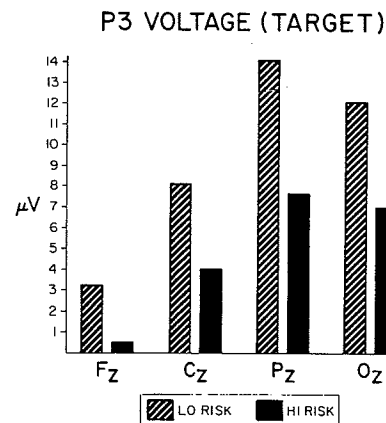

FIG. 6. Mean P3 voltage obtained to the rare target stimuli for the HR and LR groups of subjects at the four midline electrodes.

TABLE 3

FREQUENCIES SIGNIFICANTLY DIFFERENT FROM ZERO, MAGNITUDE AND PHASE SPECTRA FOR HIGH
RISK AND LOW RISK GROUPS SEPARATELY

	High Risk			Low Risk		
Hz	Mag	Phase	Frequencies Significantly Different From 0	Mag	Phase	Frequencies Significantly Different From 0
0.0	21785.5	0.0000	*	21854.4	0.0000	*
1.43	601.2	1.1729	†	1251.1	0.4391	*
2.86	233.6	−1.4475	§	424.1	−1.2474	*
4.29	81.4	−0.5027		153.2	−0.7061	¶
5.71	49.0	−0.1531		189.2	0.1329	¶
7.14	54.2	−0.7572		236.9	−0.7747	‡
8.57	49.0	1.2444		210.2	0.6078	†
10.00	23.6	−0.9015		97.0	−1.4307	*
11.43	39.4	1.1518	¶	85.7	−0.8586	§
12.86	37.7	−1.4922	§	12.5	−0.7064	
14.29	15.5	0.9973		15.0	−0.2955	
15.71	6.4	−0.3994		10.9	1.0539	
17.14	16.7	0.8424		4.8	0.7569	
18.57	15.1	1.0006		14.3	0.7382	
20.00	15.3	1.2471	¶	14.1	1.1564	
21.43	17.1	0.6264	§	15.6	1.0512	
22.86	22.3	0.6072	†	14.4	0.8668	¶
24.29	10.0	1.2600	¶	11.8	1.3195	
25.71	10.3	0.8676	§	7.6	0.8506	
27.14	9.6	0.9408	§	8.1	1.0798	
28.57	8.0	0.7658	¶	5.5	1.4212	
30.00	9.4	1.1939	§	5.6	1.0456	

*$p<0.00001$; †$p<0.0001$; ‡$p<0.001$; §$p<0.01$; ¶$p<0.05$.

used in the linear analysis were subjected to a quadratic discriminant analysis.

DISCUSSION

The present data indicate that the late positive component of the ERP differentiates boys at high risk for alcoholism from matched controls. This finding replicates our previous results [5] as well as results reported by O'Connor et al. [18]. Our current findings indicate that electrophysiological differences previously obtained between HR and LR boys do not appear to be modality or task specific. We have now demonstrated ERP differences between HR and LR boys using auditory as well as visual stimuli. Furthermore ERP differences have been obtained in a speed paradigm as well as an accuracy paradigm.

Two specific techniques for extracting salient features of ERPs are generally used. Typically most investigators record several hundred data points and characterize the ERP in the time domain as a succession of positive and negative deflections of varying amplitude and latency. With this technique the investigator limits measurements to the amplitude and latency of a few (i.e., 1–6) data points from the entire data set (i.e., 100–300). The use of basis functions in the time domain has also been applied to the analysis of ERPs. Various investigators have utilized Principal Component Analysis (PCA) to decompose the entire ERP data set

TABLE 4

PERCENTAGE CORRECT CLASSIFICATION USING THE INDICATED
FREQUENCIES (1.4, 7.1, 8.6, 11.4 Hz)

	Linear Discriminant Analyses	Quadratic Discriminant Analyses
At Risk	87%	87%
Control	78%	74%
Overall	83%	81%

into individual elementary curves which are labelled components. These elementary curves are called basis functions. The sum of the derived components should typically approximate the waveform of the measured ERP. Moreover the basis functions (i.e., PCA) must be selected so that each component represents a unique aspect of the ERP. In the case of PCA the derived "components" are independent of each other. This particular analytical approach has been shown to misallocate variance across components [17,26]. Moreover, components extracted by PCA are questionable when electrophysiological events exhibit a variable latency [16].

It has been postulated that the spatio-temporal charac-

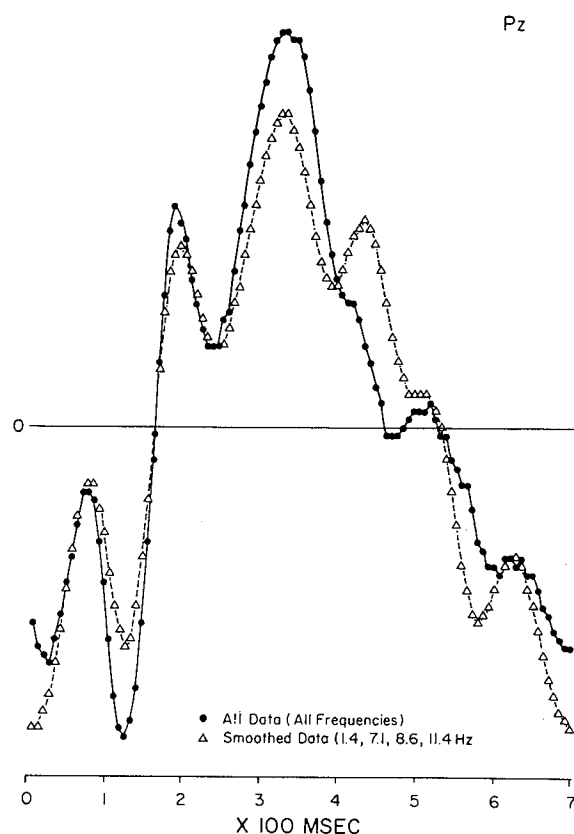### BETWEEN-GROUP MEAN FREQUENCY DIFFERENCES IN TIME DOMAIN

FIG. 7. Between-group mean frequency differences for all 21 frequencies evaluated (solid dots) and only those frequencies significantly different at the Pz electrode (1.4, 7.1, 8.6 and 11.4 Hz) (open triangles).

a range of frequencies. The identical analytical technique may also be applied to the background EEG which is known to be a prime source of the variance of the ERP. We recently described a method for constructing linear and quadratic discriminant functions in the spectral domain using a stepwise frequency selection measure [23]. A multivariate time series discrimination procedure in the frequency domain allowed us to discriminate between boys at high risk for alcoholism and matched controls. In the current study we used similar data analytic techniques in the frequency domain to differentiate new groups of high risk and control boys tested in a different experimental paradigm.

Our results indicate that statistical differences between high risk and control boys are obtained at specific frequencies. Moreover, comparisons of the first 5 target stimuli and the last 5 target stimuli revealed differences in frequency changes over time between the two groups. The linear discriminant analysis yielded an 83% overall correct classification. The quadratic discriminant analysis resulted in an overall 81% correct classification.

Studies with adoptees have demonstrated the interaction of genetic and environmental factors in the development of alcoholism and have more importantly distinguished multiple subtypes of alcoholism that have distinct genetic and environmental determinants. These data have completely vitiated the existence of etiological homogeneity in alcoholism. Prior difficulties in obtaining consistent and replicable results with biological and genetic markers in alcoholic subjects, as well as in individuals at high risk is very likely caused by the now well-established etiological heterogeneity. In our work with boys at high risk, we have specified more explicit diagnostic criteria for clinical subtypes of alcoholism and have attempted to identify biological markers which may be useful to differentiate these subtypes.

In the present study our findings indicate that significant electrophysiological differences exist between sons of alcoholic fathers and control subjects. This difference is now obtained with a new sample tested under different experimental parameters. Moreover, the neurophysiological data in the present study were obtained from sons of alcoholic fathers of Type 2 alcoholism. Our present findings replicate our previous data and extend the potential generalizability of our past observations.

teristics of neuronal events in the brain may best be understood as large numbers of coupled oscillators [11,27]. Indeed, ERPs are likely to reflect the spatio-temporal activity of vast neuronal networks, and may contain oscillatory components which require the use of basis functions in the frequency domain. The use of the Fourier transform allows the decomposition of the ERP into sets of sines and cosines over

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