0145-6008/03/2707-1064$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 27, No. 7
July 2003

Auditory P3 in Female Alcoholics

Sudha Suresh, Bernice Porjesz, David B. Chorlian, Keewhan Choi, Kevin A. Jones, Kongming Wang, Arthur Stimus, and Henri Begleiter

Background: The P3 (P300) has been considered to be a phenotypical marker of the risk for alcoholism. Although reductions in visual P3 in male and female alcoholics have been replicated, studies of auditory target P3 have been inconsistent. Our objective was to study the magnitude of auditory P3 reduction in female alcoholics and to establish the association between P3 reduction and alcoholism while taking into account comorbid depression and psychoactive drug dependence. The characteristics of P3 reduction were further examined by studying the reduction in family history–positive and –negative individuals.

Methods: Auditory target P3s recorded from 61 scalp electrodes in female alcoholics ($n = 71$) were compared with P3s from female controls ($n = 159$) ranging in age from 18 to 50 years. The amplitudes and latencies were statistically analyzed, by using repeated-measures ANOVA, in six regional electrode arrays and at representative electrode sites, with age and comorbid depression as covariates. The effects of family density and clinical variables such as depression and drug dependence were also examined with correlation analysis.

Results: Alcoholic women had significantly lower P3 amplitudes in all six regions and at midline electrode sites. The reductions were not associated with comorbid depression, as shown by low correlations and similar P3 amplitudes at Pz in female alcoholics with and without depression. The P3 amplitudes in women with a high family density were smaller than those in women with a low family density of alcohol dependence. Drug dependency did not influence P3 amplitude, as shown by similar responses in drug-dependent and non–drug-dependent alcoholic women.

Conclusions: These findings highlight the significance of P3 reductions associated with alcoholism in women, independently of comorbid depression. Family density effects further support the evidence that these findings are heritable. These results suggest that P3 can be considered as a phenotypical marker of vulnerability to alcoholism in women.

Key Words: Auditory Target P3, Female Alcoholics, Family History, Disinhibition.

ALCOHOLISM IS A complex multifactorial disease. Documented evidence is available on sexual dimorphism in the drinking pattern, drinking history, and consequences of drinking. Most of the epidemiological studies show that, compared with men, women generally start to drink later in life, consume less per occasion, and are more likely to be abstinent (York and Welte, 1994). Although the rate of alcoholism is lower in women than in men (Kessler et al., 1994), studies suggest that women are more vulnerable than men to adverse medical consequences of heavy alcoholic consumption, such as greater alcohol-related liver damage (Ashley et al., 1977; Zhang et al., 1999) and hippocampal changes (Agartz et al., 1999). These findings have been echoed by Hommer et al. (2001) and Pfefferbaum et al. (2001), who have reported differences in brain morphological deficits in men and women. The prevailing literature highlights neuroanatomical gender differences in the susceptibility to alcoholism, but it is yet to be ascertained whether such gender differences are apparent in the neurophysiological measures of processing.

A large body of evidence indicates that the heritability of alcoholism is high and varies by sex and phenotypical measures (Heath and Martin, 1991; Heath et al., 1991; Pickens et al., 1991). Family pedigree studies, twin studies, and adoption studies provide compelling evidence that implicates the role of genes in alcohol susceptibility in women and men (Prescott et al., 1994a,b). Genetic influences are present in men (51–56%) and in women (55–66%), suggesting that both genders are equally genetically vulnerable to alcoholism. Earlier studies had shown a higher prevalence of alcoholism in the daughters of alcoholic mothers than of alcoholic fathers (Cotton, 1979). Recent studies on male and female probands indicate that both genders equally transmit alcoholic tendencies to their offspring of both genders (McGue and Slutske, 1996).

Systematically reduced P3 amplitudes in alcoholic patients in populations at risk for alcoholism and evidence from twin studies have established P3 as a phenotypical marker for alcoholism (Begleiter et al., 1984; Begleiter and

From the Department Of Psychiatry, State University of New York Downstate Medical Center, Brooklyn, New York.

Received for publication September 26, 2002; accepted April 15, 2003.

Supported by NIH Grant 5 R01 AA02686 from the NIAAA.

Reprint requests: Bernice Porjesz, PhD, Department Of Psychiatry, SUNY Downstate Medical Center, 450 Clarkson Ave., Box 1203, Brooklyn, NY 11203; Fax: 718-270-4081; E-mail: bp@cns.hscbklyn.edu.

DOI: 10.1097/01.ALC.0000075549.49800.A0

Porjesz, 1995, 1999; Benegal et al., 1995; Berman et al., 1993; Hesselbrock, 1995; Hesselbrock et al., 2001; Hill et al., 1990; Hill and Steinhauer, 1993b; Porjesz and Begleiter, 1996, 1998; O'Connor et al., 1987; Ramachandran et al., 1996; van der Stelt, 1999; van der Stelt et al., 1998; Whipple et al., 1991). Results from the Collaborative Study on the Genetics of Alcoholism (COGA) study provide supportive evidence indicating the P3 heritability to be between 0.43 and 0.60 (Almasy et al., 1999; Daw et al., 1995). O'Connor et al. (1994) reported similar findings for auditory P3 in a twin study, with heritabilities ranging from 0.49 to 0.69 at posterior leads. Evidence from other twin studies reinforces these findings on the heritability of P3 amplitude (Almasy et al., 1999; Katsanis et al., 1997; van Beijsterveldt, 1996; van Beijsterveldt and van Baal, 2002; van Beijsterveldt et al., 1998; Wright et al., 2001). Significant P3 deficits in alcoholic probands, affected and unaffected relatives, and young male and female offspring from densely affected families emphasize the biological heritability in both genders (Porjesz et al., 1998). Data from the COGA project indicate that female alcoholics manifest a reduced P3 amplitude, but not to the same degree as male alcoholics. Hill and Steinhauer (1993b) also showed reduced P3 amplitudes in female alcoholics. However, the limited number of studies in women does not definitively determine the relationship between P3 amplitude and the risk of alcoholism.

When the P3 amplitude is considered as a phenotypical marker for alcohol dependence, certain issues need to be considered. It is well known that a reduced P3 amplitude is not unique to alcohol-dependent individuals or to individuals at risk for developing alcoholism. A comprehensive meta-analysis of the P3 amplitude in high-risk individuals enumerated a number of factors that alter P3 amplitude (Polich et al., 1994). Alterations in P3 amplitude have been found in various psychiatric disorders, such as schizophrenia (Blackwood et al., 1987), dementia (Ito et al., 1990; Pfefferbaum et al., 1990), major depression (Bruder et al., 1995; Yanai et al., 1997), and bipolar depression (Blackwood et al., 1996; Pierson et al., 2000; Souza et al., 1995). Regier et al. (1990) and Kessler et al. (1997) have reported that a number of disorders coexist with alcoholism. Among them, the comorbidity of alcoholism and depression is likely to remain a significant problem, because the rates of both disorders are increasing at younger ages (Burke et al., 1991; Helzer et al., 1990; Klerman and Weissman, 1989; Wittchen et al., 1994). Considering the time sequence of occurrence of these comorbid conditions, the prevalence of clinical depression that occurred before alcohol dependence was markedly low (5.3%; Gilman and Abraham, 2001; Helzer and Pryzbeck, 1988). Depression is also more prevalent among individuals with alcohol dependence than without alcohol dependence (Kessler et al., 1997; Miller et al., 1996; Schuckit et al., 1997). In a recent study, no significant differences in P3 amplitude were associated with alcoholism and depression in women. However, anxiety was found to amplify the P3 reduction associated with depression in alcoholics (Bauer et al., 2001). Therefore, studies on the heritability of alcoholism in the presence of these factors become complicated. Keeping in mind the heterogeneity of alcoholism, it needs to be established that the P3 amplitude reduction in alcoholics exists independently of these factors.

Most of the studies examining heritable traits and the effects of alcoholism on the brain have focused on male alcoholics. With the increase in the number of female alcoholics, the focus is now shifting to female alcoholics. The target P3 amplitude reduction is a frequently observed phenomenon in male alcoholics (Porjesz et al., 1980; Porjesz and Begleiter, 1983, 1996) that has been replicated across different laboratories. Earlier studies on single-trial analyses showed unequivocal P3 amplitude reductions in alcoholics (Pfefferbaum et al., 1991). However, reductions of P3 amplitude in men and women are not uniform for the auditory and visual modalities. Reductions of P3 amplitude in alcoholic men and high-risk individuals for the auditory modality were not strikingly evident (Hill et al., 1995b; Polich et al., 1988; Rodriguez Holguin et al., 1998), but significantly reduced amplitudes in both auditory and visual P3 amplitude were reported in high-risk and adult alcoholic women (Hill and Steinhauer, 1993a,b). Others have shown reductions in the amplitudes of P3 in abstinent male alcoholics in auditory oddball paradigms (Cohen et al., 1995, 2002; Patterson et al., 1987; Pfefferbaum et al., 1991) and in high-risk nonalcoholic men (Hada et al., 2001; Ramachandran et al., 1996). Parsons et al. (1990) reported amplitude deficits in adult men, but not in women. Hill et al. (1999) were unable to replicate their earlier results and attributed the P3 amplitude reduction in women to the greater prevalence of affective disorder. In women, they showed a positive correlation of P3 amplitude with depression. Recent findings from our laboratory (Prabhu et al., 2001) indicated low visual amplitude P3 in female alcoholics, but we were unable to find any significant association between the reduced visual P3 amplitude and comorbid depression. The inconsistencies in the reports could be due to variations in the sample characteristics of the alcoholic population, e.g., comorbid factors, drug and family history, task paradigms, and modality, which may suppress the differences in P3 characteristics between groups. Porjesz and Begleiter (1998) reported identical results with tasks at different levels of difficulty. Neither modality nor task difficulty had an effect on the results of P3 amplitude in alcoholics and controls (Cohen et al., 2002). Other possible co-determinants, such as psychoactive drugs, depression, and family history, are to be considered in future studies on the associations between P3 amplitude and alcoholism (Costa et al., 2000; Hill et al., 1999; Porjesz et al., 1998).

Although it has been established that male alcoholics and individuals at risk manifest reduced P3 amplitudes, this has not been examined to the same extent in women. Furthermore, reports of reduced P3 amplitude are more consistent

Table 1. Demographic and Alcohol Use Characteristics of the Sample

	Controls (n = 159)			Alcoholics (n = 71)		
Variable	Mean	SD	Range	Mean	SD	Range
Age (years)	25.21	5.00	18.4–43.4	36.99	5.77	24.84–49.5
ED (years)	15.0	2.70	0–25	11.71	3.32	0–18
DI	3.68	5.79	0–270	238.22	397.33	0–840

DI, product of the number of drinks per day × the number of drinking days in a month averaged over the last 6 months; ED, years of formal education.

in the visual than in the auditory modality (Polich et al., 1994). It has recently been demonstrated that female alcoholics manifest reduced P3 amplitudes in the visual modality (Prabhu et al., 2001), independently of depression, and that female children of alcoholics display P3 reductions similar to those of male children (Hill et al., 1990, 1995a). However, Hill et al. (1999) report that the P3 reductions in women are due to comorbid depression. Therefore, this study was undertaken to determine whether, similar to men, female alcoholics also manifest P3 deficits in the auditory modality in addition to the visual modality and whether this deficit, associated with alcoholism, is independent of depression.

METHODS

Subjects

Subjects were right-handed women aged 18 to 49 years. Female alcoholics (n = 72; mean age, 36.99 years; SD, 5.77 years) were undergoing treatment in a short-term alcohol treatment unit (Addictive Disease Hospital, Kings County Hospital Center, New York, NY). The initial diagnosis was based on DSM-III-R criteria. These subjects were in a 30-day rehabilitation program and were detoxified before the time of testing. On meeting the aforementioned criteria, each subject was invited to the laboratory, wherein she underwent a detailed psychiatric interview (by HB and BP) that focused on questions of drug and alcohol use and on psychiatric history, both for the patient and for her first- and second-degree relatives. Assignment of subjects to the category of "depressed" was based on answers to a self-report questionnaire.

The control sample (n = 159; mean age, 25.21 years; SD, 5.00 years) responded to newspaper advertisements or notices posted in the State University of New York Health Science center. Subjects were social drinkers or nondrinkers with no personal or family history of medical or psychiatric problems and without alcohol or drug dependence.

Subjects were screened with the help of self-reported answers to a questionnaire for details of alcohol and drug use, medical and psychiatric histories, and family history. The institutional review board approved the research procedures in the State University of New York study, and all subjects signed informed consent before participation. All subjects had normal or corrected-to-normal vision and were paid. Although the subjects were not given an audiometric examination, no one in either group had difficulty hearing the tones or discriminating between them. Urine tests were performed to screen out subjects with current drug use. A breath analyzer test was administered before electrophysiological recordings; individuals with values greater than 0 were excluded from the sample. Subjects with major medical problems, such as hypertension, diabetes, or endocrine disorders; those with neurological problems, such as epilepsy; those taking central nervous system (CNS) medication; those with major psychiatric disorders; and those with hearing deficits were excluded. The demographic and clinical characteristics are given in Table 1. One alcoholic outlier with a drink index of 3000 was excluded from the sample.

Experimental Design

The subject was seated comfortably in a sound-attenuated and temperature-regulated room that was dimly lit (Industrial Acoustics Co., Bronx, NY). Subjects were asked to focus on a fixation target centrally displayed on a computer monitor 1 m away. An electrocap with 61 electrodes (ECI Electro Cap International, Inc., Eaton, OH) was used that included the electrodes of the 10-20 system and 42 additional electrode sites (FPZ, AFZ, AF1, AF2, AF7, AF8, F1, F2, F5, F6, FCZ, FC1, FC2, FC3, FC4, FC5, FC6, FT7, FT8, C1, C2, C5, C6, CPZ, CP1, CP2, CP3, CP4, CP5, CP6, TP7, TP8, P1, P2, P5, P6, PO1, PO2, POZ, OZ, PO7, and PO8; electrode position nomenclature; American Electroencephalographic Association, 1991). The reference electrode was on the nose, and the ground electrode was on the forehead. The electrodes at the outer canthus and supraorbitally of the left eye monitored the horizontal and vertical eye movements. Electrode impedance was maintained at less than 5 kΩ.

Ongoing electroencephalogram activity was amplified with a gain of 10,000 by EPA2 amplifiers (Sensorium Inc., Charlotte, VT), with a bandpass of 0.02 to 50 Hz. The sampling rate was 256 Hz, with a 187.5-msec prestimulus baseline, and the activity was recorded for 1.5 sec. Digital filtering (16-Hz low-pass filter) of the raw data was performed off-line, and artifact rejection (electromyogram (EMG), electrooculogram (EOG), and saturation artifact ≥73.3 μV) was performed on-line.

Auditory Oddball Task

Subjects were presented binaurally with two tones of different frequencies. One stimulus was a low tone (600 Hz) and the other a high tone (1600 Hz) produced by a tone generator. Each stimulus had a 60-msec duration (10-msec rise and fall times and 40-msec plateau) and an intensity level of 60-dB (sound pressure level). A computer initiated the stimulus. The probabilities of the rare and the frequent tones were 0.125 and 0.875. The designation of the low or high tone as the rare (target) and frequent (nontarget) tone was alternated across the subjects. The auditory stimuli were presented through headphones (model ER-3A Tubephone Insert Earphones, 50-Ω impedance; Etymotic Research, Elk Grove Village, IL); the earpiece and a short length of the Tubephone were fitted under the electrode cap, and the individual left and right transducer cases were situated on either side of the neck.

Subjects were verbally instructed to suppress their eye blinks and to sit as still as possible. They were asked to respond to the target with a button press as quickly as possible, but not at the expense of accuracy. Subjects received a maximum of 400 trials with a uniform interstimulus interval of 1500 msec. The response time and error rates were recorded.

Only correct trials without eye artifacts were included in the average event-related potentials (ERPs). For each subject, the target P3 was obtained as the largest peak in a latency window (250–450 msec) defined as ±100 msec from the peak of the grand mean averaged waveform. The average ERPs derived from the target stimulus in the rare condition were analyzed with an automatic peak detection program. Peak amplitude was measured relative to the prestimulus baseline, and latency was measured from the time of stimulus onset.

Statistical Methods

Subject Characteristics. The two subject groups were compared with respect to each of their characteristics, i.e., demographic features, (age, education, and prevalence of alcohol or drug dependency), drink index (DI; product of the number of drinks in a day times the frequency of drinking days in a month averaged over the last 6 months), and incidence of depression (comorbidity). One-way ANOVA was used to evaluate group difference on each of these characteristics (variables), such as age, education, comorbid depression, drug dependence, and DI.

Primary Analysis. For the primary statistical analyses of the 2 subject groups (alcoholic and control), each of the 2 dependent measures—P3 amplitude and latency—was analyzed twice: first across all 61 electrode sites and then for each of the 6 regions representing the frontal, central,

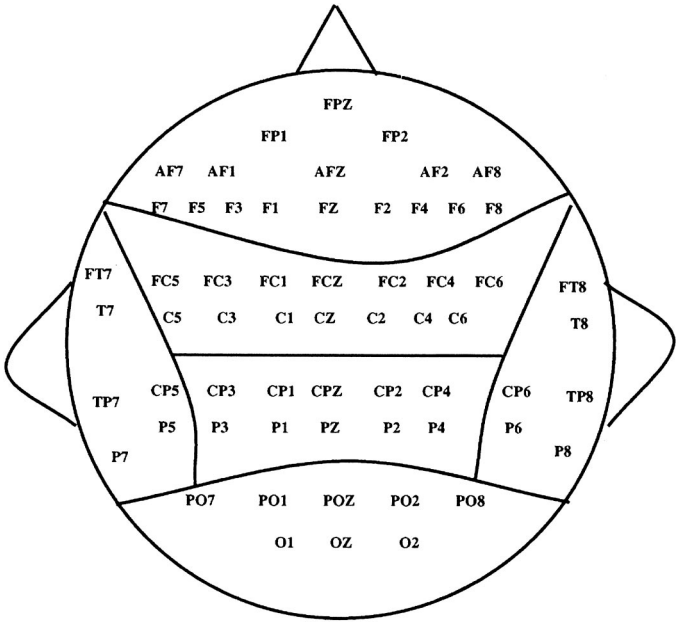

Fig. 1. The recording electrode ($n = 61$) montage and six regional groupings used in the statistical analyses.

parietal, occipital, right temporal, and left temporal brain areas. The electrode montage and the regional groupings are shown in Fig. 1.

Each of the two dependent measures was analyzed with repeated-measures analysis of variance (RMANOVA; SAS version 8.0, SAS Institute, Cary, NC) with group (alcoholic and control) as the independent measure, with age and comorbid depression as covariates, and with electrode site as the repeated measure.

Supplementary Analysis. Supplementary analysis of RMANOVA was also conducted on each of the representative midline electrodes and for an age-matched subsample of alcoholics and controls. Sample (Pearson's) correlation coefficients between P3 amplitude and comorbid depression and between P3 amplitude and family density were tested for significance in the presence of alcoholism. To study the effect of depression on P3 amplitude in the presence of alcoholism, the difference between two subgroups of female alcoholics (alcoholics with depression versus alcoholics without depression) was analyzed by using analysis of covariance with age as a covariate. Although the subjects recruited into the study were in an alcoholism rehabilitation/recovery program, some of them had histories of drug abuse; therefore, the P3 amplitude between alcoholics with a drug abuse history and those without a history of drug abuse was compared by using a one-way ANOVA to see whether the severity of drug use affected the P3 responses in the alcoholic group.

RESULTS

The subject groups differed significantly in their demographic characteristics (age, education, and prevalence of alcohol or drug dependency), DI (product of the number of drinks in a day times the frequency of drinking days in a month averaged over the last 6 months; Table 1), and incidence of depression (Table 2). The prevalence of comorbid depression in the female alcoholics was 31.9% as compared with 8.8% in the control women. The number of alcoholic women taking psychoactive drugs was 59 (81.9%), as compared with only 6 (3.8%) in the controls.

Table 2. Frequency Distribution of Clinical Characteristics

	Controls		Female alcoholics	
Variable	Frequency	%	Frequency	%
Comorbid depression				
Depression	14.0	8.8	23.0	31.9
Without depression	145.0	91.9	49.0	68.1
Suicide attempt				
Suicide attempts	2.0	1.3	16.0	22.2
No attempts	157.0	98.7	56.0	77.8
Drug abuse				
Drug dependent	6.0	3.8	59.0	81.9
Nondrug dependent	153.0	96.2	13.0	18.0
Family density				
High	NA	NA	21.0	31.34
Low			46.0	68.66

NA, not applicable; control subjects with a family history of alcoholism were excluded from the sample.

Primary Analyses

Task Performance. Group differences in task performance were evaluated by using a one-way ANOVA with age as a covariate. The response time was not statistically significant between the two groups (controls: 432 msec; SD, 107 msec; alcoholics: 436 msec; SD, 110 msec). However, the percentage error rate was significantly different in the two groups. Alcoholic individuals had a higher error rate (9.4%; SD, 14.3%) than the control group (3.8%; SD, 8.06%).

P3 Amplitude and Latency. Group-averaged waveforms showing differences in amplitude over all 12 representative electrode sites are illustrated in Fig. 2. P3 latency did not show any significant differences between alcoholic women and controls, either by multivariate ANOVA or RMANOVA.

The results from RMANOVA across all 61 sites and for each of the 6 regional electrode arrays are shown in Tables 3 and 4. There was a significant group (main) effect for P3 amplitude across all 61 sites and for each of the 6 regions. The pattern of P3 amplitude reduction in the representative midline electrodes was similar to that in the regional arrays, indicating a global P3 amplitude reduction in the female alcoholics (Table 5).

Post Hoc Analyses

Pearson's correlation coefficient of lifetime depression with P3 amplitude in female alcoholics did not show any significant values, with the exception of the frontal leads (Fz: $r = 0.23$, $p < 0.056$; F3: $r = 0.265$, $p < 0.03$). Comparisons of P3 amplitude in the alcoholic population between the drug-dependent and non–drug-dependent subgroups did not reveal any significant differences.

A separate analysis to validate the results was attempted by examining the relationship of P3 in the two groups in an age-matched sample for the regional and individual electrode sites. Significant group (main) effects (Tables 6 and 7) were seen when the effect of comorbid depression was statistically removed. The amplitude decrease was more prominent at the anterior regions, with the most significant

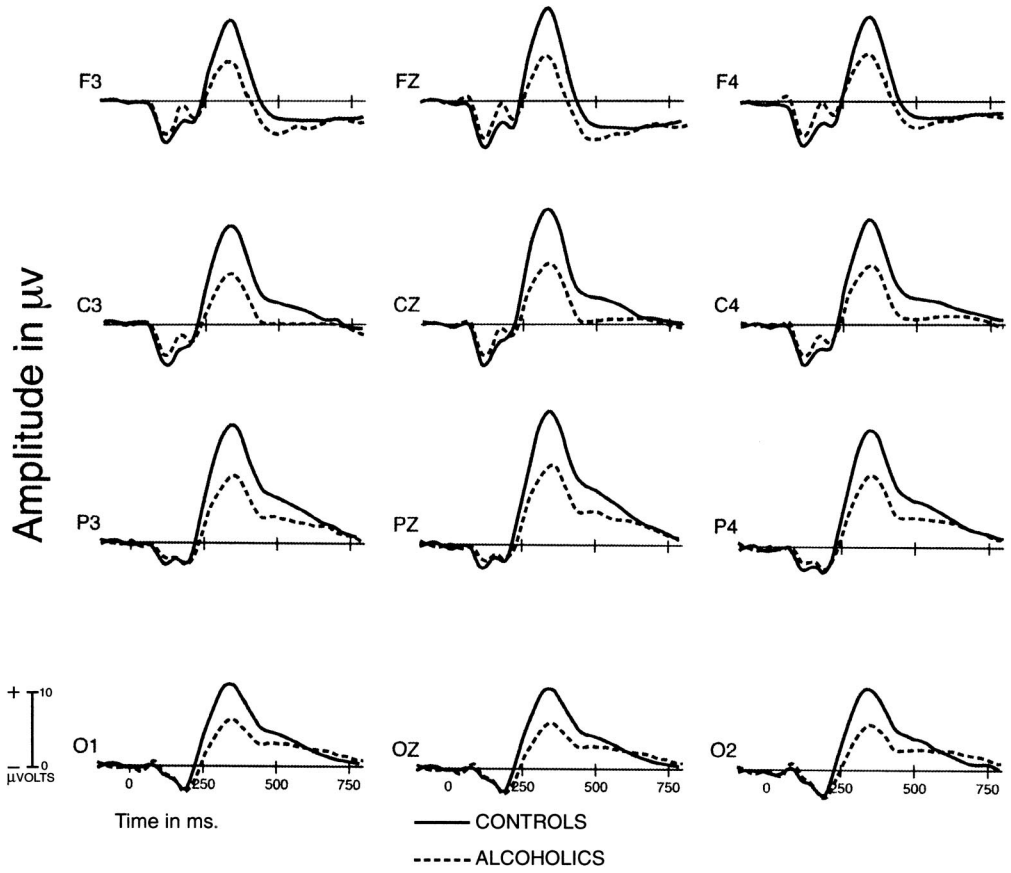

Fig. 2. Grand mean waveforms of P3 ERPs to the target stimulus for the female control and alcoholic groups over representative frontal, parietal, and occipital electrodes.

Table 3. Comparisons of Regional P3 Amplitudes for Female Alcoholics and Controls Using Repeated-Measures Analysis of Variance With Age and Comorbid Depression as Covariates

Region	*df*	*F*	*p*
Frontal	1,211	13.12	0.0004
Central	1,219	33.33	0.0001
Parietal	1,224	25.59	0.0001
Right temporal	1,224	19.19	0.0001
Left temporal	1,224	12.96	0.0004
Occipital	1,224	18.4	0.0001

Table 4. Comparison of Global and Regional P3 Amplitude for Female Alcoholics and Controls, Using Multivariate ANOVA with Age as a Covariate

Region	*df*	*F*	*p*
Global	61,173	1.82	<0.0014
Frontal	17,217	4.77	<0.0001
Central	14,220	4.86	<0.0001
Parietal	10,224	6.41	<0.0001
Right temporal	6,226	6.92	<0.0001
Left temporal	6,228	8.89	<0.0001
Occipital	8,226	6.71	<0.0001

Table 5. Mean P3 Amplitude (μV) of the Target Response at the Selected Electrodes and the Results of Analysis of Covariance with Age and Comorbid Depression as Covariates[a]

	Controls (n = 156)		Alcoholics (n = 67)			
Electrode	Mean	SD	Mean	SD	*F*	*p*
Fz	16.64	8.06	9.34	7.26	28.62	0.0001
F4	15.30	7.05	9.38	6.22	33.91	0.0001
F3	14.37	6.88	8.30	6.33	24.5	0.0001
Cz	20.58	8.23	12.07	7.67	15.51	0.0001
C3	17.40	7.41	10.04	7.09	16.71	0.0001
C4	18.48	7.62	11.31	7.07	11.83	0.0004
P3	20.33	7.86	12.65	6.72	5.27	0.0215
P4	20.58	7.87	13.61	6.92	8.26	0.0046
Pz	23.13	8.73	14.98	7.54	4.67	0.0275
O2	14.76	6.89	9.59	6.17	3.96	0.0402
O1	14.84	6.99	9.79	6.45	1.21	0.2431
OZ	14.87	6.75	9.44	6.24	2.46	0.09

[a] *df* = 1,219.

group difference occurring in the frontal and central regions and at the frontal and central midline electrodes.

Alcoholism, Depression, Drug Dependence, and Family Density. The criteria for the subgrouping of low-density (LD) and high-density (HD) families were that for the LD group, subjects had one alcoholic relative or no first-degree alcoholic relatives, and for the HD group, subjects had two or more first-degree alcoholic relatives. The demographic characteristics (age and education) of the HD and LD subgroups of alcoholics, as well as their respective DIs, are presented in Table 8; there were no significant differences between the subgroups in terms of age, education, or DI, although there was a tendency for the HD group to have a higher DI. Examining midline leads, correlation analyses revealed a negative correlation of P3 amplitude with family

Table 6. Comparisons of Regional P3 Amplitudes for Female Alcoholics and Controls for a Representative Age-Matched Subsample (Control: $n = 36$; Mean Age, 31.63 years; SD, 3.35 years; Alcoholics: $n = 33$; Mean Age, 32.85 years; SD, 3.08 years) Using Repeated-Measures ANOVA with Comorbid Depression as Covariate[a]

Variable	*F*	*p*
Frontal	15.91	0.0002
Central	10.53	0.0018
Parietal	6.58	0.0126
Occipital	4.1	0.0468
Right temporal	1.5	0.2249
Left temporal	6.87	0.0109

[a] $df = 1,67$.

Table 7. Mean P3 Amplitude (μV) of the Target Response at the Selected Electrodes in an Age-Matched Subsample and the Comparisons of the P3 Amplitude Using Analysis of Covariance With Depression as the Covariate[a]

	Controls ($n = 36$)		Female alcoholics ($n = 33$)			
Electrode	Mean	SD	Mean	SD	*F*	*p*
Fz	17.21	8.77	8.91	5.98	18.31	0.0001
F3	15.12	7.43	7.61	5.16	19.99	0.0001
F4	15.73	8.12	8.86	5.98	14.24	0.0003
Cz	19.12	9.39	12.71	7.28	9.09	0.0036
C3	16.55	8.18	10.93	5.61	10.36	0.002
C4	16.98	8.54	11.98	6.55	6.04	0.0166
Pz	21.07	8.73	15.99	7.82	5.52	0.0219
P3	18.95	7.78	13.36	6.60	8.45	0.0050
P4	18.64	7.23	14.74	7.34	4.75	0.0328
OZ	13.73	6.44	10.48	6.52	5.52	0.0218
O1	13.05	6.28	10.74	6.62	2.91	0.0929
O2	13.40	6.64	10.66	6.50	4.17	0.0452

[a] $df = 1,67$.

Table 8. Demographic and Alcohol Use Characteristics in the High-Density (HD) and Low-Density (LD) Alcoholic Subsamples

	HD ($n = 21$)			LD ($n = 46$)		
Variable	Mean	SD	Range	Mean	SD	Range
Age (years)	38.16	6.15	24.84–48.38	36.51	5.71	25.63–49.08
ED (years)	12.0	3.86	0–18	11.50	3.22	0–16
DI	266.5	267.1	0–840	168.2	193.9	0–750

HD, two or more first-degree alcoholic relatives; LD, one first-degree alcoholic relative or none.

density for Cz ($r = -0.314$; $p < 0.01$) and Pz ($r = -0.24$; $p < 0.049$). This was supported by the results of repeated measures in regional areas and univariate analysis at the individual electrode sites. The overall group main effect was significant when age and comorbid depression were used as covariates. Alcoholics from HD families had significantly decreased amplitudes in central ($p < 0.0085$), parietal ($p < 0.0464$), and right temporal ($p < 0.0254$) regions (Table 9) when age and comorbid depression were used as covariates.

No significant differences were seen in the subset of female alcoholics with depression in comparison to the female alcoholics without depression [Cz: $F(1,69) = 3.195$, $p < 0.078$; Pz: $F(1,69) = 0.187$, $p < 0.67$]. Similar P3 responses were also observed in a two-group comparison between those codependent on drugs compared with those without drug dependency.

Table 9. Comparisons of Regional P3 Amplitudes of the Alcoholic Subsample of High-Density Versus Low-Density Subjects Using Repeated-Measures ANOVA With Age and Comorbid Depression as Covariates[a]

Region	*F*	*p*
Frontal	1.4	0.2415
Central	7.4	0.0085
Parietal	4.13	0.0464
Occipital	0.58	0.4493
Right temporal	5.25	0.0254
Left temporal	1.25	0.2676

[a] $df = 1,63$.

DISCUSSION

This study demonstrated significant P3 reductions in female alcoholics in all six regional electrode arrays when the effects of age and comorbid depression were statistically removed. The speed of processing as indexed by P3 latency and response time was not affected in the female alcoholics, although they had a higher error rate. The correlation coefficient tests between P3 amplitude and lifetime depression did not show any significant results for central and posterior leads but revealed moderate association only for the left frontal lead and a weak correlation for the midline frontal lead. The P3 amplitude reduction was not different between drug-dependent and non–drug-dependent subgroups in the alcoholic population. The reduction in P3 amplitude was greater in female alcoholics from families with a strong family history (HD) compared with those with little or no family history of alcoholism (LD). These results indicate that the significant P3 reduction in female alcoholics is not due to confounders such as age and comorbid depression. These findings suggest that low P3 amplitude in the auditory modality can be considered as a potential endophenotypical marker of alcoholism in female alcoholics, as in men.

P3 and Alcoholism

Reductions in P3 amplitude in alcoholics in this study are consistent with the wealth of data reported from this laboratory, as well as others (Begleiter and Porjesz, 1995; Cohen et al., 1995, 1997, 2002; Glenn et al., 1994, 1996; Hada et al., 2000; Miyazato and Ogura, 1993; Pfefferbaum et al., 1991; Porjesz et al., 1980, 1987, 1998; Prabhu et al., 2001; Realmuto et al., 1993). Most of the studies reporting P3 amplitude reductions have used visual and auditory paradigms in men. Prabhu et al. (2001), in their study of female alcoholics, used a more difficult visual paradigm in comparison to the simple auditory task used here. However, the results from both of these studies from our laboratory indicate significant P3 amplitude reductions in female alcoholics, independent of comorbid factors such as depression and drug abuse. From these observations, one can conclude that neither modality nor level of task difficulty can account for P3 deficits in female alcoholics. One limitation in most studies reporting on chronic alcoholics is that they have used few recording sites. Studies from our

laboratory have reported results from 61 electrodes. The results of P3 reductions from the 61 electrode positions and the representative electrodes indicate a global reduction of P3 amplitude in female alcoholics.

P3 Amplitude Reduction and Psychopathology

In a few reports, the P3 amplitude reduction was attributed to comorbid factors. Cognitive processes are often impaired in major depression (Silberman et al., 1983). Yet there have been no consistent findings on the P3 amplitude reduction (Blackwood et al., 1987; Yanai et al., 1997) in depression. Alcohol dependence and major depression often occur together (Deykin et al., 1987; Grant and Harford, 1995; Regier et al., 1990); the prevalence of major depression is higher in female alcoholics than in male alcoholics (Hill et al., 1999).

The results of this study support the notion that alcoholism is the major factor that determines the reduced P3 amplitude. Significant reductions in P3 amplitude in midline and regional arrays persisted when depression and age were included in the analysis as covariates. This further demonstrates the similarity in P3 responses between the subpopulation of alcoholics with depression and those without depression. Furthermore, neither drug abuse history nor drinking pattern altered the results. Post hoc comparisons demonstrated that the significant P3 amplitude reduction between the control and alcoholic female groups persisted when depression was included in the analysis. The results of this study are contrary to those of Hill et al. (1999), who reported significant P3 amplitude reductions at Pz only in female alcoholics with depression. Their sample was drawn from families with HD of alcoholism and additional psychological features, such as anxiety (panic attack), drug dependence, and antisocial personality. The authors were unable to replicate the results in men due to nonavailability of an adequate sample of male alcoholics with depression.

The discrepancies in the results may be due to differences in the criteria used for the classification of lifetime depression and the differences in the subject characteristics. Our sample of alcoholics (23 with depression and 49 without depression) included subjects with positive and negative family histories of alcoholism. Earlier studies from our laboratory on female alcoholics have also shown reductions in visual P3 amplitude that were not attributed to comorbid depression (Prabhu et al., 2001). This suggests that the ERP differences between female alcoholics and controls are related to alcoholism independently of depression. This conclusion is also supported by incidental observations from other studies. P3 amplitude reductions associated with depression seem to be reversible, as shown by the normal P3 amplitudes in patients after recovery from depression (Gangadhar et al., 1993; Yanai et al., 1997). In contrast, reports on P3 amplitude reduction in alcoholics have not reported the reversibility of the P3 deficits during prolonged abstinence or in recovered alcoholics (Porjesz and Begleiter, 1985), despite the recovery of brainstem auditory evoked responses. This suggests that low P3 is a "trait" rather than a "state" characteristic; this is supported by studies reporting the prevalence of low P3 amplitudes in the sons and daughters of alcoholics (Begleiter et al., 1984; Polich et al., 1994).

Our study suggests that the drug abuse that coexists in alcoholics may not be a contributing factor, because there were no significant amplitude differences between the alcoholic subsamples with and without drug abuse. However, it is difficult to rule out the drug effects on the decreased P3 response in our study because the number of nonusers was small. The work of Bauer (2001) has shown that compared with healthy controls, all drug-dependent groups showed similar P3 amplitude decrements regardless of drug (e.g., cocaine, cocaine and alcohol, and opioids) and that the number of drugs did not affect P3 amplitude. The work of Bauer (2001) has shown that P3 amplitude in psychoactive drug–dependent groups did not differ from that of patients on cocaine and alcohol. In contrast to our sample of only women, their sample included both men and women. From the data available from self-reporting questionnaires in our study, subjects who were dependent on drugs and alcohol had consumed medium to large quantities of one or more types of psychoactive drugs. Even among drug users, the severity of drug use, defined by the quantity and the number of drugs used, did not affect P3 amplitude. The results imply that the P3 amplitude reduction in women is associated with alcoholism, independent of drug use; this is contrary to the hypothesis that the combined effects of drugs and alcohol are synergistic and more detrimental to the brain.

Antisocial personality disorder (ASPD) and conduct disorder traits are known to coexist with alcohol and drug dependence in children and adults (Weinberg et al., 1998; Wilens et al., 1994) in both clinical and community samples (Helzer and Pryzbeck, 1988; Hesselbrock and Hesselbrock, 1997). However, gender-based differences in the prevalence of these comorbidities have been reported (Bucholz et al., 2000; Cale and Lilienfeld, 2002). Studies in COGA have found that conduct disorder and ASPD are present only among the most severe female alcoholics ($<7.9\%$), whereas the prevalence is much higher among men (74.6%). ASPD and conduct disorder also tend to be more prevalent in the most severe male alcoholics. Because the incidence of symptoms of ASPD was so low in the sample of women in this study, it was not examined.

P3 and Family History

Family history is an important co-determining factor for vulnerability to alcoholism (Porjesz and Begleiter, 1998). Familial risk of alcoholism in first-degree relatives

indicates a 7-fold increase in vulnerability (Goldman, 1993). Results on the family history of alcoholism have well established that P3 amplitude is a highly heritable trait and is considered as a biological phenotypical marker (Hada et al., 2000; Hill and Steinhauer, 1993a,b; Porjesz et al., 1998; Ramachandran et al., 1996). Pfefferbaum et al. (1991) also reported the P3 amplitude to be a function of the number of first-degree relatives and not of any drinking history variable. Female alcoholic subjects from LD and HD families in this study were similar in the quantity of alcohol intake. The DI, as a covariate, eliminated the possibly confounding effect of the amount of alcohol consumption. The results in this study clearly indicate that the P3 amplitude reductions are not due to the neurotoxic effects of alcohol or drugs. In this sample, the HD female alcoholics who had more first-degree alcoholic relatives and were severe alcoholics showed significantly greater P3 amplitude reductions. LD female alcoholics had significantly lower amplitudes as compared with nonalcoholic female controls, although they were somewhat higher than those of the HD group. The pattern and magnitude of amplitude changes provide evidence that the severity of alcohol dependence determined by the family history is inversely related to the P3 amplitude. Our findings of P3 reductions associated with family history support the view that genetic factors/family history contribute further to the group differences in P3 amplitude in women and men (Cohen et al., 1995). The genetic factors contributing to P3 reduction come from investigations on alcoholics and their relatives and from twin studies (Almasy et al., 1999; Katsanis et al., 1997; O'Connor et al., 1994; Porjesz and Begleiter, 1998; van Beijsterveldt et al., 1998; van Beijsterveldt and van Baal, 2002; Wright et al., 2001). It is interesting to note that the central and parietal region show even greater P3 amplitude decreases in family history–positive individuals. A previous report from our laboratory that used a similar paradigm and modality showed surface energy reduction localized to the central and parietal regions in male alcoholics (Cohen et al., 1995). It is interesting to note that this study demonstrated that female alcoholics showed similar abnormalities. The results also concur with the report of Hill and Steinhauer (1993b), who reported a significant reduction at Pz in female alcoholics. Their sample was drawn from HD families, and the probands were family history positive for alcoholism. Prabhu et al. (2001) showed significant P3 reductions at the central and frontal regions in a female alcoholic sample that included both family history–positive and family history–negative individuals, but the percentage of family history–positive individuals was higher. The authors were unable to show differences between family history–positive and –negative subjects in a visual paradigm.

P3, Alcoholism, and CNS Disinhibition

Many investigators have proposed that the P3 is largely caused by a widely distributed inhibitory event that operates under various processing functions (Halgren et al., 1986; Rockstroh et al., 1992; Woodward et al. 1991). This indicates that P3 reflects an inhibitory process, namely, a disfacilitated state of the neuronal networks. It is widely accepted that ERPs are a composite activity of intracortical currents induced by excitatory and inhibitory postsynaptic potentials. CNS excitation, inhibition, and homeostasis are responsible for a stable affective state, as well as for complex cognitive processes.

It is plausible to conclude that the P3 reduction in the female alcoholics reflects low levels of inhibitory activity, as it does in men. Begleiter and Porjesz (1999) have hypothesized that the low P3 amplitude is an index of CNS disinhibition and is inherited in the predisposition for developing alcoholism. This state of underlying CNS disinhibition, or hyperexcitability, leads to subsequent exposure to alcohol in an effort to temporarily alleviate this condition; drinking behavior can serve to normalize this CNS hyperexcitability. However, with repeated chronic alcohol exposures, it ultimately leads to physical dependence and an exacerbation of CNS hyperexcitability during withdrawal episodes.

The P3 amplitude reduction reported from our laboratory in adult female alcoholics for both the auditory and visual modalities establishes it as an important neurobiological marker for alcoholism in women. The high correlation of P3 amplitude with family density suggests the heritability of the P3 amplitude in women, as well as in men. It is beyond the scope of this article to speculate on the exact cause of the neurophysiological dysfunction that undoubtedly exists in female alcoholics, but the results suggest that the P3 amplitude reduction in female alcoholics is heritable and independent of comorbid depression or psychoactive drugs. Additional longitudinal studies in high-risk women are under way to further support the hypothesis.

ACKNOWLEDGMENTS

The authors thank Carlene Haynes, Aquanette Sass, Joyce Alonzia, Debra Josephson, Edward Babington, Aleksey Dumer, and Alyson Wahl.

REFERENCES

Agartz I, Momenan R, Rawlings RR, Kerich MJ, Hommer DW (1999) Hippocampal volume in patients with alcohol dependence. Arch Gen Psychiatry 56:356–363.

Almasy L, Porjesz B, Blangero J, Chorlian DB, O'Connor SJ, Kuperman S, Rohrbaugh J, Bauer LO, Reich T, Polich J, Begleiter H (1999) Heritability of event-related brain potentials in families with a history of alcoholism. Am J Med Genet 88:383–390.

American Electroencephalographic Association (1991) American Electroencephalographic Society guidelines for standard electrode position nomenclature. J. Clin Neurophysiol 8:200–202.

Ashley MJ, Olin JS, le Riche WH, Kornaczewski A, Schmidt W, Rankin JG (1977) Morbidity in alcoholics. Evidence for accelerated development of physical disease in women. Arch Intern Med 137:883–887.

Bauer LO (2001) CNS recovery from cocaine, cocaine and alcohol, or opioid dependence: a P3 study. Clin Neurophysiol 112:1508–1515.

Bauer LO, Costa L, Hesselbrock VM (2001) Effects of alcoholism, anxiety and depression on P300 in women: a pilot study. J Stud Alcohol 62:571–579.

Begleiter H, Porjesz B (1995) Neurophysiological phenotypic factors in the development of alcoholism, in *Alcohol and Alcoholism, Vol 1: The Genetics of Alcoholism* (Begleiter H, Kissin B eds), pp 269–293. Oxford University Press, New York.

Begleiter H, Porjesz B (1999) What is inherited in the predisposition toward alcoholism? A proposed model. Alcohol Clin Exp Res 23:1125–1135.

Begleiter H, Porjesz B, Bihari B, Kissin B (1984) Event-related brain potentials in boys at risk for alcoholism. Science 225:1493–1496.

Benegal V, Jain S, Subbukrishna DK, Channabasavanna SM (1995) P3 amplitudes vary inversely with continuum of risk in first degree male relatives of alcoholics. Psychiatr Genet 5:149–156.

Berman SM, Whipple SC, Fitch RJ, Noble EP (1993) P3 in young boys as a predictor of adolescent substance use. Alcohol 10:69–76.

Blackwood DH, Sharp CW, Walker MT, Doody GA, Glabus MF, Muir WJ (1996) Implications of comorbidity for genetic studies of bipolar disorder: P3 and eye tracking as biological markers for illness. Br J Psychiatry 30:85–92.

Blackwood DH, St Clair DM, Blackburn IM, Tyrer GM (1987) Cognitive brain potentials and psychological deficits in Alzheimer's dementia and Korsakoff's amnesic syndrome. Psychol Med 17:349–358.

Bruder GE, Tenke CE, Stewart JW, Towey JP, Leite P, Voglmaier M, Quitkin FM (1995) Brain event-related potentials to complex tones in depressed patients: relations to perceptual asymmetry and clinical features. Psychophysiology 32:373–381.

Bucholz KK, Hesselbrock VM, Heath AC, Kramer JR, Schuckit MA (2000) A latent class analysis of antisocial personality disorder symptom data from a multi-centre family study of alcoholism. Addiction 95:553–567.

Burke KC, Burke JD Jr, Rae DS, Regier DA (1991) Comparing age at onset of major depression and other psychiatric disorders by birth cohorts in five US community populations. Arch Gen Psychiatry 48: 789–795.

Cale EM, Lilienfeld SO (2002) Sex differences in psychopathy and antisocial personality disorder. A review and integration. Clin Psychol Rev 22:1179–1207.

Cohen HL, Ji J, Chorlian DB, Begleiter H, Porjesz B (2002) Alcohol-related ERP changes recorded from different modalities: a topographic analysis. Alcohol Clin Exp Res 26:303–317.

Cohen HL, Porjesz B, Begleiter H, Wang W (1997) Neurophysiological correlates of response production and inhibition in alcoholics. Alcohol Clin Exp Res 21:1398–1406.

Cohen HL, Wang W, Porjesz B, Begleiter H (1995) Auditory P3 in young alcoholics: regional response characteristics. Alcohol Clin Exp Res 19:469–475.

Costa L, Bauer L, Kuperman S, Porjesz B, O'Connor S, Hesselbrock V, Rohrbaugh J, Begleiter H (2000) Frontal P3 decrements, alcohol dependence, and antisocial personality disorder. Biol Psychiatry 47:1064–1071.

Cotton NS (1979) The familial incidence of alcoholism: a review. J Stud Alcohol 40:89–116.

Daw EW, Rice JP, Reich T, Porjesz B, Begleiter H (1995) Relationship of ERPs in COGA control families (poster 149). Psychiatr Genet 5:S78.

Deykin EY, Levy JC, Wells V (1987) Adolescent depression, alcohol and drug abuse. Am J Public Health 77:178–182.

Gangadhar BN, Ancy J, Janakiramaiah N, Umapathy C (1993) P3 amplitude in non-bipolar, melancholic depression. J Affect Disord 28:57–60.

Gilman SE, Abraham HD (2001) A longitudinal study of the order of onset of alcohol dependence and major depression. Drug Alcohol Depend 63:277–286.

Glenn S, Parsons OA, Sinha R (1994) Assessment of recovery of electrophysiological and neuropsychological functions in chronic alcoholics. Biol Psychiatry 36:443–452.

Glenn SW, Parsons OA, Smith LT (1996) ERP responses to target and nontarget visual stimuli in alcoholics from VA and community treatment programs. Alcohol 13:85–92.

Goldman D (1993) Recent developments in alcoholism: genetic transmission. Recent Dev Alcohol 11:231–248.

Grant BF, Harford TC (1995) Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. Drug Alcohol Depend 39:197–206.

Hada M, Porjesz B, Begleiter H, Polich J (2000) Auditory P3a assessment of male alcoholics. J Biol Psychiatry 48:276–286.

Hada M, Porjesz B, Chorlian DB, Begleiter H, Polich J (2001) Auditory P3a deficits in male subjects at high risk for alcoholism. Biol Psychiatry 49:726–738.

Halgren E, Stapleton JM, Smith M, Altafullah I (1986) Generators of the human scalp P3s, in *Evoked Potentials* (Cracco RQ, Bodis Wollner I eds), pp 269–286. Alan Liss, New York.

Heath AC, Martin NG (1991) The inheritance of alcohol sensitivity and of patterns of alcohol use. Alcohol Alcohol 1:141–145.

Heath AC, Meyer J, Jardine R, Martin NG (1991) The inheritance of alcohol consumption patterns in a general population twin sample: II. Determinants of consumption frequency and quantity consumed. J Stud Alcohol 52:425–433.

Helzer JE, Canino GJ, Yeh EK, Bland RC, Lee CK, Hwu HG, Newman S (1990) Alcoholism—North America and Asia. A comparison of population surveys with the Diagnostic Interview Schedule. Arch Gen Psychiatry 47:313–319.

Helzer JE, Pryzbeck TR (1988) The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. J Stud Alcohol 49:219–224.

Hesselbrock MN, Hesselbrock VM (1997) Gender, alcoholism and comorbidity, in *Gender and Alcohol* (Wilsnack R, Wilsnack S eds), pp 49–71. Rutgers Center of Alcohol Studies, Piscataway, NJ.

Hesselbrock V, Begleiter H, Porjesz B, O'Connor S, Bauer L (2001) P300 event-related potential amplitude as an endophenotype of alcoholism—evidence from the collaborative study on the genetics of alcoholism. J Biomed Sci 8:77–82.

Hesselbrock VM (1995) The genetic epidemiology of alcoholism, in *The Genetics of Alcoholism* (Begleiter H, Kissin B eds), pp 17–39. Oxford University Press, New York.

Hill SY, Locke J, Steinhauer SR (1999) Absence of visual and auditory P3 reduction in nondepressed male and female alcoholics. Biol Psychiatry 46:982–989.

Hill SY, Muka D, Steinhauer S, Locke J (1995a) P3 amplitude decrements in children from families of alcoholic female probands. Biol Psychiatry 38:622–632.

Hill SY, Steinhauer S, Locke J (1995b) Event-related potentials in alcoholic men, their high-risk male relatives, and low-risk male controls. Alcohol Clin Exp Res 19:567–576.

Hill SY, Steinhauer S, Park J, Zubin J (1990) Event-related potential characteristics in children of alcoholics from high density families. Alcohol Clin Exp Res 14:6–16.

Hill SY, Steinhauer SR (1993a) Assessment of prepubertal and postpubertal boys and girls at risk for developing alcoholism with P3 from a visual discrimination task. J Stud Alcohol 54:350–358.

Hill SY, Steinhauer SR (1993b) Event-related potentials in women at risk for alcoholism Alcohol 10:349–354.

Hommer D, Momenan R, Kaiser E, Rawlings R (2001) Evidence for a gender-related effect of alcoholism on brain volumes. Am J Psychiatry 158:198–204.

Ito J, Yamao S, Fukuda H, Mimori Y, Nakamura S (1990) The P3 event-related potentials in dementia of the Alzheimer type. Correla-

tions between P3 and monoamine metabolites. Electroencephalogr Clin Neurophysiol 77:174–178.

Katsanis J, Iacono WG, McGue MK, Carlson SR (1997) P3 event-related potential heritability in monozygotic and dizygotic twins. Psychophysiology 34:47–58.

Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC (1994) Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry 54:313–321.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS (1997) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 51:8–19.

Klerman GL, Weissman MM (1989) Increasing rates of depression (review). JAMA 261:2229–2235.

McGue M, Slutske W (1996) The inheritance of alcoholism in women. NIAAA Res Monogr 32:65–91.

Miller NS, Klamen D, Hoffmann NG, Flaherty JA (1996) Prevalence of depression and alcohol and other drug dependence in addictions treatment populations. J Psychoactive Drugs 28:111–124.

Miyazato Y, Ogura C (1993) Abnormalities in event-related potentials: N100, N200 and P3 topography in alcoholics. Jpn J Psychiatry Neurol 47:853–862.

O'Connor S, Hesselbrock V, Tasman A, DePalma N (1987) P3 amplitudes in two distinct tasks are decreased in young men with a history of paternal alcoholism. Alcohol 4:323–330.

O'Connor S, Morzorati S, Christian JC, Li T-K (1994) Heritable features of the auditory oddball event-related potential: peaks, latencies, morphology and topography. Electroencephalogr Clin Neurophysiol 92: 115–125.

Parsons OA, Sinha R, Williams HL (1990) Relationships between neuropsychological test performance and event-related potentials in alcoholic and nonalcoholic samples. Alcohol Clin Exp Res 14:746–755.

Patterson BW, Williams HL, McLean GA, Smith LT, Schaeffer KW (1987) Alcoholism and family history of alcoholism: effects on visual and auditory event-related potentials. Alcohol 4:265–274.

Pfefferbaum A, Desmond JE, Galloway C, Menon V, Glover GH, Sullivan EV (2001) Reorganization of frontal systems used by alcoholics for spatial working memory: an fMRI study. Neuroimage 14:7–20.

Pfefferbaum A, Ford JM, Kraemer HC (1990) Clinical utility of long latency 'cognitive' event-related potentials (P3): the cons. Electroencephalogr Clin Neurophysiol 76:6–12.

Pfefferbaum A, Ford JM, White PM, Mathalon D (1991) Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. Alcohol Clin Exp Res 15:839–850.

Pickens RW, Svikis DS, McGue M, Lykken DT, Heston LL, Clayton PJ (1991) Heterogeneity in the inheritance of alcoholism. A study of male and female twins. Arch Gen Psychiatry 48:19–28.

Pierson A, Jouvent R, Quintin P, Perez-Diaz F, Leboyer M (2000) Information processing deficits in relatives of manic depressive patients. Psychol Med 30:545–555.

Polich J, Haier RJ, Buchsbaum M, Bloom FE (1988) Assessment of young men at risk for alcoholism with P3 from a visual discrimination task. J Stud Alcohol 49:186–190.

Polich J, Pollock VE, Bloom FE (1994) Meta-analysis of P3 amplitude from males at risk for alcoholism. Psychol Bull 115:55–73.

Porjesz B, Begleiter H (1983) Brain dysfunction and alcohol, in *The Biology of Alcoholism, Vol 7: The Pathogenesis of Alcoholism—Biological Factors* (Kissin B, Begleiter H eds), pp 425–483. Plenum, New York.

Porjesz B, Begleiter H (1985) The use of event-related potentials in the study of alcoholism: implications for the study of drugs of abuse. NIDA Res Monogr 62:77–99.

Porjesz B, Begleiter H (1996) Effects of alcohol on electrophysiological activity of the brain, in *Alcohol and Alcoholism, Vol 2: The Pharmacology of Alcohol and Alcohol Dependence* (Begleiter H, Kissin B eds), pp 207–247. Oxford University Press, New York.

Porjesz B, Begleiter H (1998) Genetic basis of event-related potentials and their relationship to alcoholism and alcohol use. J Clin Neurophysiol 15:44–57.

Porjesz B, Begleiter H, Bihari B, Kissin B (1987) Event-related brain potentials to high incentive stimuli in abstinent alcoholics. Alcohol 4:283–287.

Porjesz B, Begleiter H, Garozzo R (1980) Visual evoked potential correlates of information processing deficits in chronic alcoholics. Adv Exp Med Biol 126:603–623.

Porjesz B, Begleiter H, Reich T, Van Eerdewegh P, Edenberg HJ, Foroud T, Goate A, Litke A, Chorlian DB, Stimus A, Rice J, Blangero J, Almasy L, Sorbell J, Bauer LO, Kuperman S, O'Connor SJ, Rohrbaugh J (1998) Amplitude of visual P3 event-related potential as a phenotypic marker for a predisposition to alcoholism: preliminary results from the COGA Project. Collaborative Study on the Genetics of Alcoholism. Alcohol Clin Exp Res 22:1317–1323.

Prabhu VR, Porjesz B, Chorlian DB, Wang K, Stimus A, Begleiter H (2001) Visual p3 in female alcoholics. Alcohol Clin Exp Res 25:531–539.

Prescott CA, Hewitt JK, Heath AC, Truett KR, Neale MC, Eaves LJ (1994a) Environmental and genetic influences on alcohol use in a volunteer sample of older twins. J Stud Alcohol 55:18–33.

Prescott CA, Hewitt JK, Truett KR, Heath AC, Neale MC, Eaves LJ (1994b) Genetic and environmental influences on lifetime alcohol-related problems in a volunteer sample of older twins. J Stud Alcohol 55:184–202.

Ramachandran G, Porjesz B, Begleiter H, Litke A (1996) A simple auditory oddball task in young adult males at high risk for alcoholism. Alcohol Clin Exp Res 20:9–15.

Realmuto G, Begleiter H, Odencrantz J, Porjesz B (1993) Event-related potential evidence of dysfunction in automatic processing in abstinent alcoholics. Biol Psychiatry 33:594–601.

Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK (1990) Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 264:2511–2518.

Rockstroh B, Muller M, Cohen R, Elbert T (1992) Probing the functional brain state during P3-evocation. J Psychophysiol 6:175–184.

Rodriguez Holguin S, Corral M, Cadaveira F (1998) Visual and auditory event-related potentials in young children of alcoholics from high- and low-density families. Alcohol Clin Exp Res 22:87–96.

Schuckit MA, Tipp JE, Bucholz KK, Nurnberger JI Jr, Hesselbrock VM, Crowe RR, Kramer J (1997) The life-time rates of three major mood disorders and four major anxiety disorders in alcoholics and controls. Addiction 92:1289–1304.

Silberman EK, Weingartner H, Post RM (1983) Thinking disorder in depression. Arch Gen Psychiatry 40:775–780.

Souza VB, Muir WJ, Walker MT, Glabus MF, Roxborough HM, Sharp CW, Dunan JR, Blackwood DH (1995) Auditory P3 event-related potentials and neuropsychological performance in schizophrenia and bipolar affective disorder. Biol Psychiatry 37:300–310.

van Beijsterveldt CE, Molenaar PC, de Geus EJ, Boomsma DI (1998) Individual differences in P300 amplitude: a genetic study in adolescent twins. Biol Psychol 47:97–120.

van Beijsterveldt CEM, van Baal GCM (2002) Twin and family studies of the human electroencephalogram: a review and a meta-analysis. Biol Psychol 61:111–138.

van Beijsterveldt T (1996) *The Genetics of Electrophysiological Indices of Brain Activity: An EEG Study in Adolescent Twins*. Universiteit Van Amsterdam, Amsterdam.

van der Stelt O (1999) Visual P3 as a potential vulnerability marker of alcoholism: evidence from the Amsterdam study of children of alcoholics. European Society for Biomedical Research on Alcoholism. Alcohol Alcohol 34:267–282.

van der Stelt O, Geesken R, Gunning WB, Snel J, Kok A (1998) P3 scalp topography to target and novel visual stimuli in children of alcoholics. Alcohol 15:119–136.

Weinberg NZ, Rahdert E, Colliver JD, Glantz MD (1998) Adolescent substance abuse: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 37:252–261.

Whipple SC, Berman SM, Noble EP (1991) Event-related potentials in alcoholic fathers and their sons. Alcohol 8:321–327.

Wilens TE, Biederman J, Spencer TJ, Frances RJ (1994) Comorbidity of attention-deficit hyperactivity and psychoactive substance use disorders. Hosp Community Psychiatry 45:421–435.

Wittchen HU, Knauper B, Kessler RC (1994) Lifetime risk of depression. Br J Psychiatry Suppl 26:16–22.

Woodward SH, Brown WS, Marsh JT, Dawson ME (1991) Probing the time-course of the auditory oddball P3 with secondary reaction time. Psychophysiology 28:609–618.

Wright MJ, Hansell NK, Geffen GM, Geffen LB, Smith GA, Martin NG (2001) Genetic influence on the variance in P3 amplitude and latency. Behav Genet 31:555–565.

Yanai I, Fujikawa T, Osada M, Yamawaki S, Touhouda Y (1997) Changes in auditory P3 in patients with major depression and silent cerebral infarction. J Affect Disord 46:263–271.

York JL, Welte JW (1994) Gender comparisons of alcohol consumption in alcoholic and nonalcoholic populations. J Stud Alcohol 55: 743–750.

Zhang Y, Kreger BE, Dorgan JF, Splansky GL, Cupples LA, Ellison RC (1999) Alcohol consumption and risk of breast cancer: the Framingham Study revisited. Am J Epidemiol 149:93–101.