

Event-related potentials and comorbidity in alcohol-dependent adult males

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Abstract

The present study examined event-related potentials (ERPs) elicited by a visual discrimination task in a community sample of adult males with a lifetime diagnosis of alcohol dependence. Study participants were subtyped by the presence of additional comorbid disorders (antisocial personality, depression, and drug abuse or dependence). In all groups of alcohol-dependent subjects, even those without any additional comorbid disorders, P3 amplitude differed from that of a comparison group. Alcohol-dependent subjects with a diagnosis of illicit drug abuse or dependence, especially if they had antisocial personality as well, had the smallest amplitude responses. The amplitude profile of the P3 across the parietal electrodes used as active sites was flattened among alcoholic subjects, with P3 amplitude disproportionately reduced at the midline. Among alcoholic subjects with a lifetime diagnosis of depression, the flattened amplitude profile was due to elevated mean amplitude of the P3 at lateral leads, especially P4, relative to the comparison group. Alterations in ERP responses appear to be a general characteristic of alcoholism in men, although the presence of other comorbid disorders, particularly drug abuse or dependence together with antisocial personality, results in the greatest reductions in P3 amplitude.

Descriptors: Event-related potentials, Alcoholism, Comorbidity, Antisocial personality, Drug abuse and dependence, Depression

A number of studies have been conducted in the past 20 years examining event-related potentials (ERPs) in alcoholic men, especially since the seminal article by Begleiter, Porjesz, Bihari, and Kissin (1984). Although the specific findings have varied somewhat from one study to the next, the most robust finding has been that the P3 wave of the ERP is reduced in amplitude among alcoholic men (Cohen, Wang, Porjesz, & Begleiter, 1995; Emmerston, Dustman, Shearer, & Chamberlin, 1987; Glenn, Parsons, & Smith, 1996; Patterson, Williams, McLean, Smith, & Schaeffer, 1987; Pfefferbaum, Ford, White, & Mathalon, 1991; Pfefferbaum, Rosenbloom, & Ford, 1987; Porjesz, Begleiter, Bihari, & Kissin, 1987; Realmuto, Begleiter, Odencrantz, & Porjesz, 1993; Whipple, Berman, & Noble, 1991). Together with the relatively consistent findings that P3 amplitude is reduced among male children of alcoholic men (Begleiter et al., 1984; O'Connor, Hesselbrock, Tasman, & DePalma, 1987; Porjesz & Begleiter, 1996; Ramachandran, Porjesz, Begleiter, & Litke, 1996; Ramsey & Finn, 1997; van der Stelt, Geesken, Gunning, Snel, & Kok, 1998; Whipple et al., 1991; see review by Polich, Pollock, & Bloom, 1994), this has led to suggestions that P3 amplitude can serve as a marker of genetic risk for alcoholism (Porjesz & Begleiter, 1996) or that reduced P3

amplitude is an endophenotype associated with risk for a spectrum of disorders in males, including externalizing and substance use disorders (Iacono, 1998).

It is much less clear, however, how reduced amplitude of the P3 might relate to comorbidity among alcoholism and other psychiatric disorders. Yet comorbidity is more the rule than the exception, whether in the general population (Kessler, Crum, Warner, Nelson, et al., 1997) or in clinical samples of alcoholics. For instance, a recent study conducted in Germany reported that 58% of a sample of hospitalized alcohol-dependent individuals had an additional Axis I or Axis II disorder as well (Driessen, Veltrup, Wetterling, John, & Dilling, 1998). Another recent study, conducted in the northeastern United States, found that an identical percentage of adult men and women in one of eight inpatient or outpatient alcohol treatment programs met DSM-III-R criteria for at least one additional psychiatric disorder (Morgenstern, Langenbucher, Labouvie, & Miller, 1997). Although the rate of comorbidity is lower in the general population than among individuals in treatment or seeking treatment (Regier et al., 1990), it is nevertheless a central feature of alcoholism.

In fact, comorbidity is a central feature of attempts to develop typologies of alcoholism (Babor et al., 1992; Cloninger, 1987). A consistent thread in such typologies is that drinking problems are associated either with characterological problems, such as under-socialized behavior, externalizing tendencies, and antisocial personality, or with emotional disturbances, such as depression and anxiety, leading to Cloninger's suggestion of separate genetic pathways to alcoholism.

Despite the importance of comorbidity in many conceptualizations of alcoholism, especially in relation to antisocial personality,

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the ERP literature has not directly addressed this issue. Bauer, Hesselbrock, O'Connor and colleagues have examined the relative influences on ERPs of a family history for alcoholism and an individual history of antisocial personality (e.g., Bauer & Hesselbrock, 1999; Bauer, O'Connor, & Hesselbrock, 1994; O'Connor, Bauer, Tasman, & Hesselbrock, 1994), but these studies have focused on nonalcoholic subjects. Many studies of alcoholic subjects have used medical or neurological disease as an exclusion criterion but have not explicitly addressed psychiatric comorbidity, although authors of at least one study noted the prevalence of such disorders in their sample (Realmuto et al., 1993). Several studies have excluded subjects with "any psychiatric disorders" (e.g., Cohen et al., 1995; Emmerson et al., 1987; Whipple et al., 1991). Although on the face of it, studies in this latter category cast doubt on Cloninger's (1987) assertion that reduced amplitude of the P3 is associated with Type II alcoholism, of which antisocial personality is a key feature, it is not at all clear that such studies excluded subjects with all forms of antisocial personality, such as conduct disorder or adult-onset antisocial tendencies. In so far as reduced P3 amplitude is associated with a spectrum of externalizing disorders in adult and adolescent males (Bauer & Hesselbrock, 1999; Iacono, 1998), one cannot determine from the extant literature whether externalizing disorders are as central to the reduction in P3 amplitude observed among alcoholic men as they are to conceptualizations of alcoholism.

The principal contribution of the present study consists in examining aspects of the ERP in a community sample of alcoholic men subtyped by comorbidity. It is possible thus to determine whether alcoholism per se is associated with reduced P3 amplitude or other alterations in ERP characteristics or whether, conversely, co-occurrence of an additional psychiatric disorder, such as antisocial personality, is a requisite feature of the P3 effect in alcoholism. In addition, using mutually exclusive groups of alcohol-dependent men allowed us to determine how specific types of comorbidity affect the ERPs of alcoholic men, a strategy not often used to identify the effects of comorbidity and the role of specific disorders.

The current study also adds to the existing literature by studying alcohol-dependent men drawn from a large community-based, statewide sample broadly representative of middle-aged men in Minnesota. As indicated previously, the vast majority of ERP studies examining the effects of alcoholism have been conducted with treatment samples or samples of individuals who are treatment bound. Such samples are likely to be biased in terms of the types of other psychiatric disorders observed and are not likely to be representative of the population as a whole. Epidemiological studies such as the present one are therefore extremely important in helping to characterize the full range of variability in ERP characteristics among alcoholic men.

The present report derives from the study of Holdcraft, Iacono, and McGue (1998), which examined the course and severity of alcoholism, the extent of drug use, and personality characteristics of alcoholic men drawn from a community sample as a function of comorbidity. In this paper, we extend the findings of Holdcraft and colleagues by examining characteristics of visual ERPs in a subset of their sample.

Method

Participants

The sample consisted of adult male participants in the Minnesota Twin Family Study (MTFS), a community-based epidemiological

investigation of the origins and development of substance use disorders and related psychopathology. Subjects were biological fathers or stepfathers of male twins from two age cohorts, one representing twin births in the state of Minnesota between 1971 and 1975 and the other representing similar births between 1978 and 1982. (See Iacono, Carlson, Taylor, Elkins, & McGue, 1999, and Iacono, Lykken, & McGue, 1996, for comprehensive descriptions of the sample and study design.)

Alcohol-dependent subjects in the present sample were a subset of those studied by Holdcraft et al. (1998). All met criteria for alcohol dependence or alcoholism by one of several major diagnostic systems: DSM-III (American Psychiatric Association, 1980), DSM-III-R (American Psychiatric Association, 1987), Feighner Criteria (Feighner et al., 1972), or Research Diagnostic Criteria (RDC) (Spitzer, Endicott, & Robins, 1978). Subjects were grouped on the basis of presence and nature of any comorbid diagnoses. One group, the pure group ($n = 20$), consisted of "pure" alcoholics, who met criteria for alcohol dependence or alcoholism but not any other disorders assessed by the study: antisocial personality, conduct disorder, major depressive disorder, illicit drug abuse or dependence, and nicotine dependence. A second group ($n = 16$) consisted of alcoholics with comorbid major depression but without antisocial personality disorder or conduct disorder (MDD group). Subjects with alcohol dependence and a comorbid antisocial personality disorder but without major depression were grouped on the basis of presence of a diagnosis of illicit drug abuse or dependence; those in one group ($n = 10$) had at least one such diagnosis (ASPD/drug group), whereas those in the other group ($n = 14$) did not (ASPD group). A fifth group ($n = 19$) consisted of alcoholics with at least one diagnosis of illicit drug abuse or dependence but without antisocial personality, conduct disorder, or a major depressive disorder (drug group).

A total of 79 participants from the sample of Holdcraft et al. (1998) were eligible for inclusion in one of the five groups of alcohol-dependent subjects and had comparable ERP data. In addition, we selected a group of comparison subjects ($n = 47$) at random from among all men in the larger sample without any of the diagnoses controlled in the alcohol-dependent subjects: alcohol dependence, illicit drug abuse or dependence, antisocial personality, conduct disorder, major depression, and nicotine dependence. After subjects with neurological disease (one), poor task performance (seven), aberrant ERP data (one), or excessive artifact (three) had been excluded, as described below, the final sample consisted of 115 subjects. The size and demographic characteristics of the various groups are given in Table 1.

The pure, MDD, ASPD, and ASPD/drug groups have been carefully characterized in terms of alcohol and drug use, severity of alcoholism, and personality measures (Holdcraft et al., 1998). In brief, subjects in the two ASPD groups combined tended to have an earlier onset of drinking to intoxication and a more chronic and severe course of alcoholism than subjects in the MDD or pure groups. Because the groups of alcohol-dependent subjects in the present study are subsets of the groups reported on by Holdcraft and colleagues and have been grouped somewhat differently, we have included in Table 1 measures of their alcohol use history together with demographic data.

Interview and Diagnostic Procedure

After written informed consent had been obtained from participants, alcohol and psychoactive substance use was assessed by means of a modified version of the expanded Substance Abuse Module (SAM; Robins, Babor, & Cottler, 1987). As mentioned

Table 1. Group Sizes, Demographic Characteristics, and Drinking History

Variable	Alcohol group							Total	F or χ^2 Statistic
	Control	Pure	MDD	ASPD	ASPD/Drug	Drug			
N	40	19	15	13	9	19	115		
Age	41.5 (5.8)	40.7 (5.8)	41.7 (3.8)	41.5 (6.3)	40.0 (4.2)	37.9 (5.1)	40.7 (5.1)	1.56	
Right-handers (%)	85.0	73.7	93.3	84.6	77.8	84.2	81.4	2.67	
Years education	14.6 (2.5)	14.6 (2.5)	14.7 (2.5)	12.9 (1.5)	13.6 (2.1)	12.5 (3.3)	14.0 (2.6)	2.83*	
Occupation	3.4 (1.7)	3.4 (1.8)	3.3 (2.0)	4.8 (1.3)	4.0 (1.9)	4.0 (1.6)	3.7 (1.7)	1.87	
MAST analog	1.3 (0.7)	3.2 (1.2) ^{ab}	5.2 (2.7)	6.5 (3.6) ^a	5.2 (2.7)	5.5 (3.1) ^b	3.7 (2.9)	3.33*	
Family history (%)	17.5	36.8	22.2	45.5	22.2	47.4	29.3	3.92	
Age first intoxicated	19.9 (5.0)	18.1 (2.2) ^{ab}	17.1 (3.0)	15.5 (3.2) ^a	14.8 (2.8) ^b	16.0 (1.6)	17.4 (3.7)	3.87*	
Number intoxications	9 (32)	86 (134) ^{abc}	217 (311)	487 (448) ^a	463 (357) ^b	348 (341) ^c	195 (311)	4.77**	
Intoxication years	6.0 (7.5)	15.3 (7.7) ^a	20.2 (6.7)	21.5 (8.7)	23.6 (5.0) ^a	18.5 (6.0)	14.7 (9.7)	2.28*	
Maximum consumption	8.4 (5.8)	16.6 (6.2)	24.9 (13.0)	30.1 (16.4)	26.0 (12.0)	23.4 (15.4)	18.4 (13.5)	2.25	

Note: Groups sharing the same superscript differ significantly by post hoc comparisons of means. Family history represents the presence of alcohol problems in at least one first-degree male relative. Occupational level is coded according to Hollingshead (1957), with 1 representing the highest and 7 the lowest. For continuous variables, means are given, with standard deviations in parentheses. The test statistic is an *F* ratio in the case of continuous variables, χ^2 in the case of proportions. Comparisons of organismic characteristics (age, handedness) and demographic characteristics (years of education, occupation) include all groups. *F* ratios have 5 and 109 *df*; the test for the proportion of right-handers is a χ^2 with 5 *df* and *N* = 115. Comparisons of drinking history and severity include only the alcohol-dependent groups. *F* ratios have 4 and 70 *df*. The test for differences in the proportion of problem drinkers is a χ^2 with 4 *df* and *N* = 75; the test for differences in the proportion of subjects with a positive family history of alcohol problems is a χ^2 with 4 *df* and *N* = 73 (this information was missing for two ASPD subjects).

p* < .05. *p* < .01.

previously, criteria from four diagnostic systems were used to assess alcoholism. All other disorders were assessed according to DSM-III-R criteria. An interview designed by MTFs staff was used to assess antisocial personality. We used the Structured Clinical Interview for DSM-III-R (SCID; Spitzer, Williams, Gibbon, & First, 1992) to assess the presence of lifetime depression. The organic and bereavement rule-outs had to be satisfied for subjects to receive a diagnosis of depression. That is, there could not be any organic factor, including substance use, responsible for the onset or maintenance of the depressive state and the subject's depressed mood could not be due to simple bereavement.

A consensus, "best-estimate" approach (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982) was used to assign study diagnoses. Reliability coefficients for the various disorders assessed were satisfactory (Holdcraft et al., 1998).

Drinking severity. We derived a measure of severity of drinking roughly analogous to the Michigan Alcoholism Screening Test (MAST; Selzer, 1971). Eighteen items on the SAM are very similar in content to items on the MAST, and when combined, therefore, appear to have face validity as an analog of the MAST. Given associations between the MAST and arrests for driving while intoxicated (Zung & Charalampous, 1975) and even morbidity among inpatient alcoholics (Farragher & Webb, 1991), it seemed reasonable to use this MAST analog as a measure of drinking severity. The 18 items, each requiring a yes or no response, assess a variety of potentially problematic behaviors (e.g., physical fights when drinking, drinking before noon, inability to stop drinking, arrests for driving under the influence of alcohol), difficulties with close relationships and important responsibilities (e.g., marital problems, complaints or worries on the part of close relatives, neglecting obligations, losing a job, losing friends), subjective concerns (e.g., feeling guilty), medical complications (e.g., loss of memory for previous evening, delirium tremens, cirrhosis, hallucinations), and seeking treatment. We summed the items to

obtain a measure of drinking severity (Kuder-Richardson estimate of internal consistency equal to 0.81). Group means on this measure of severity of drinking are given in Table 1.

The other measures of drinking history appearing in Table 1 represent single items on the SAM. Presence of family history of alcohol problems among first-degree male relatives was also assessed by means of a family history interview developed by MTFs staff. Eight items assess problems related to drinking, such as physical fights, legal, financial, medical, family, school or work problems, and loss of friends. A ninth item asks whether a given family member has received treatment for alcoholism. If a subject reported that a given male relative had at least two problems or had ever been treated for alcoholism, paternal family history was coded as positive.

Psychophysiological Assessment

Recording procedure. All participants completed the assessment at approximately the same time in the afternoon. They sat in a comfortable high-backed chair while electroencephalographic (EEG) data were recorded from three parietal scalp locations, one on the midline (Pz) and one over each hemisphere (P3 and P4). Linked earlobes served as reference and an electrode on the right shin as ground. Blinks and eye movements were recorded by means of a pair of biopotential electrodes arranged in a transverse montage, one electrode superior to the right eye and the other over the outer canthus. A Grass Model 12A Neurodata acquisition system was used to collect EEG data, with each signal passed through an amplifier with a passband of 0.01 to 30 Hz (half-amplitude) and a roll-off of 18 dB per octave. For each trial, 2 s of EEG, including a 500-ms prestimulus baseline, were digitized to 12-bits resolution at a rate of 256 Hz.

ERP task. We used the rotated-heads oddball paradigm of Begleiter et al. (1984). Each of the 240 stimuli comprising this task were presented on a computer screen for 98 ms, with the intertrial

interval (ITI) varying randomly between 1 and 2 s. A small dot, which subjects were instructed to fixate, appeared in the center of the screen during the ITI. On two-thirds of the trials, participants saw a plain oval; they were instructed not to respond to these ovals. On the remaining third of the trials, participants saw a superior view of a stylized head, with the nose and one ear depicted. Participants were required to press one of two microswitches affixed to each arm of their chair to indicate whether the ear was on the left side of the head or the right. Half of these "target" trials consisted of heads with the nose pointed up, such that the left ear would be on the left side of the head as it appeared to the subject (easy discrimination). Half consisted of heads rotated 180° so that the nose pointed down, such that the left ear would appear on the right side of the screen and the right ear would appear on the left side of the screen (hard discrimination).

Performance and other subject exclusions. Participants who failed to respond correctly on better than 80% of trials in a given condition and better than 90% overall were not included in the final sample characterized in Table 1. As a result, six subjects (four in the control group, one in each of the pure and MDD groups) were excluded from analyses (and Table 1). One potential control subject with unusual ERP features was excluded because a Q-type principal components analysis of target waveforms from Pz yielded a component on which this subject alone loaded highly, indicating that he was an outlier with respect to wave shape. We excluded one potential ASPD/drug subject with multiple sclerosis. An additional ASPD subject did not complete the task.

Data preprocessing. Trials that, on visual inspection, contained excessive muscle or other artifacts were excluded from averaging. If participants failed to respond on a given trial, or if any of the EEG signals exceeded the range of the A-D converter during a given trial, the trial was repeated. We excluded trials from averaging that were repeated three or more times. One potential control subject's data were consistently contaminated by button-press artifact, another's by large EKG artifacts, and a third's by large rolling eye movements suggestive of drowsiness. All were excluded from the sample. We used the procedure of Gratton, Coles, and Donchin (1983) to correct for blinks and other ocular artifacts in the EEG.

We digitally filtered the average ERPs using a frequency-sampled FIR low-pass filter with least-squared error and a transition band (Parks & Burrus, 1987). This filter introduced no phase shift and had a cutoff frequency (down 3 dB) of approximately 8 Hz (7.94 Hz) and attenuation of 20 dB at 11 Hz. Three trained individuals identified the major components of each waveform with the assistance of a computer algorithm to identify positive or negative peaks in the waveform within a given time interval. We defined the P3 as the most prominent positive peak between 300 and 750 ms. If the waveform consisted of two peaks in this interval of approximately equal amplitude, suggesting separate P3a and P3b peaks (Squires, Squires, & Hillyard, 1975), we selected the second. The N1 was defined as the first prominent negative peak between 70 and 320 ms. The P2 and N2 often consisted of deflections in the waveform rather than true peaks. We defined the P2 as the most prominent positive peak or deflection between 110 and 470 ms and occurring before the P3 and the N2 as the most prominent negative peak or deflection after the N1 and occurring between 150 and 540 ms. In some individual averages, an early peak or deflection was not identifiable within the appropriate time interval. This occurred infrequently, for 134 of the more than 4,000

components (3.2%), most often in the case of the P2 (1.2%) or the N2 (1.8%). The P3, however, could always be identified. Measures of peak amplitude were taken in relation to the mean prestimulus activity.

Statistical analyses. After a preliminary analysis of variance (ANOVA), described in detail below, indicated that subject groups failed to respond differentially to heads differing in orientation, we reduced the data by averaging together both target types. Each ERP component was thus treated by means of a repeated-measures ANOVA, with group as the between-subjects factor and condition (target or nontarget) and lead (Pz, P3, or P4) as within-subjects factors. We examined both multivariate and univariate test statistics, with univariate probabilities for tests of the lead factor corrected by means of the Greenhouse–Geisser procedure to compensate for violations of the compound symmetry assumption required by repeated-measures ANOVAs and using Pillai's approximate or exact *F* statistic for multivariate analyses, owing to its greater robustness compared with other multivariate test statistics (Olson, 1976). Multivariate and univariate test statistics agreed in every case but one unplanned post hoc analysis; to simplify presentation of the results, we will give only the multivariate statistics. Eta squared (η^2) is provided as a measure of effect size (Rosenthal, 1994). It can be interpreted as roughly similar to the square of a correlation coefficient in that both η^2 and r^2 indicate the proportion of variance accounted for by a statistic. In the case of η^2 , it is the proportion of variance accounted for by an ANOVA factor. Because P3 amplitude most often is greatest at the midline, and to facilitate comparison of the present results with results of other studies, we also analyzed Pz separately.

Monte Carlo studies indicate that limiting the number of post hoc contrasts to the number of degrees of freedom for the effect in question maintains the nominal error rate (Carmer & Swanson, 1968, and Bernhardson, 1975, cited in Wilkinson, 1989). We therefore followed up significant group effects by means of pairwise comparisons of each alcohol-dependent group with the control group. Significant Group \times Condition or Group \times Lead interactions were followed up by means of interaction contrasts. We assessed associations between measures of substance use and P3 amplitude in response to target stimuli by means of Pearson correlation coefficients and Kendall's τ correlation coefficients, as the distribution of use measures typically deviated from normal.

Results

Severity of Drinking

Analyses comparing the five groups of alcohol-dependent subjects on measures of drinking severity and use history are summarized in Table 1, including the relevant test statistics. A significant difference among groups was evident with respect to severity of drinking, age when first intoxicated, total number of times intoxicated, and number of years drinking to the point of intoxication. Pairwise contrasts using Hayter's modification of Fisher's LSD procedure (Seaman, Levin & Serlin, 1991), which uses the studentized range statistic to preserve the nominal error rate, indicated that the pure group differed from the ASPD group on age when first intoxicated, number of lifetime intoxications, and the MAST analog measure of drinking severity, from the ASPD/drug group on age when first intoxicated, number of lifetime intoxications, and number of years drinking to the point of intoxication, and from the drug group on the MAST analog measure of severity and number of lifetime intoxi-

cations. All significant differences thus involved a comparison of the pure group with one of the comorbid groups.

ERP Measures

Grand mean waveforms for Pz are presented in Figure 1 and mean amplitudes and latencies of all components are given in Table 2.

As is evident in Figure 1, average ERPs in response to the two types of target stimuli were very similar to each other in all six groups, and responses to the two target types tended to differ from the responses to neutral stimuli (plain ovals). Given the relatively

small size of some of the groups in this study, we investigated the feasibility of reducing the number of dependent variables by collapsing the two discrimination conditions (easy or hard discrimination) into a single target condition by means of two preliminary ANOVAs, with amplitude and latency of the P3 as the respective dependent measures. In both cases, group served as the between-subjects factor and discrimination difficulty (easy or hard) and lead (Pz, P3, or P4) as within-subjects factors. Significant interactions between group and discrimination difficulty or between group, discrimination difficulty, and lead would suggest that the groups

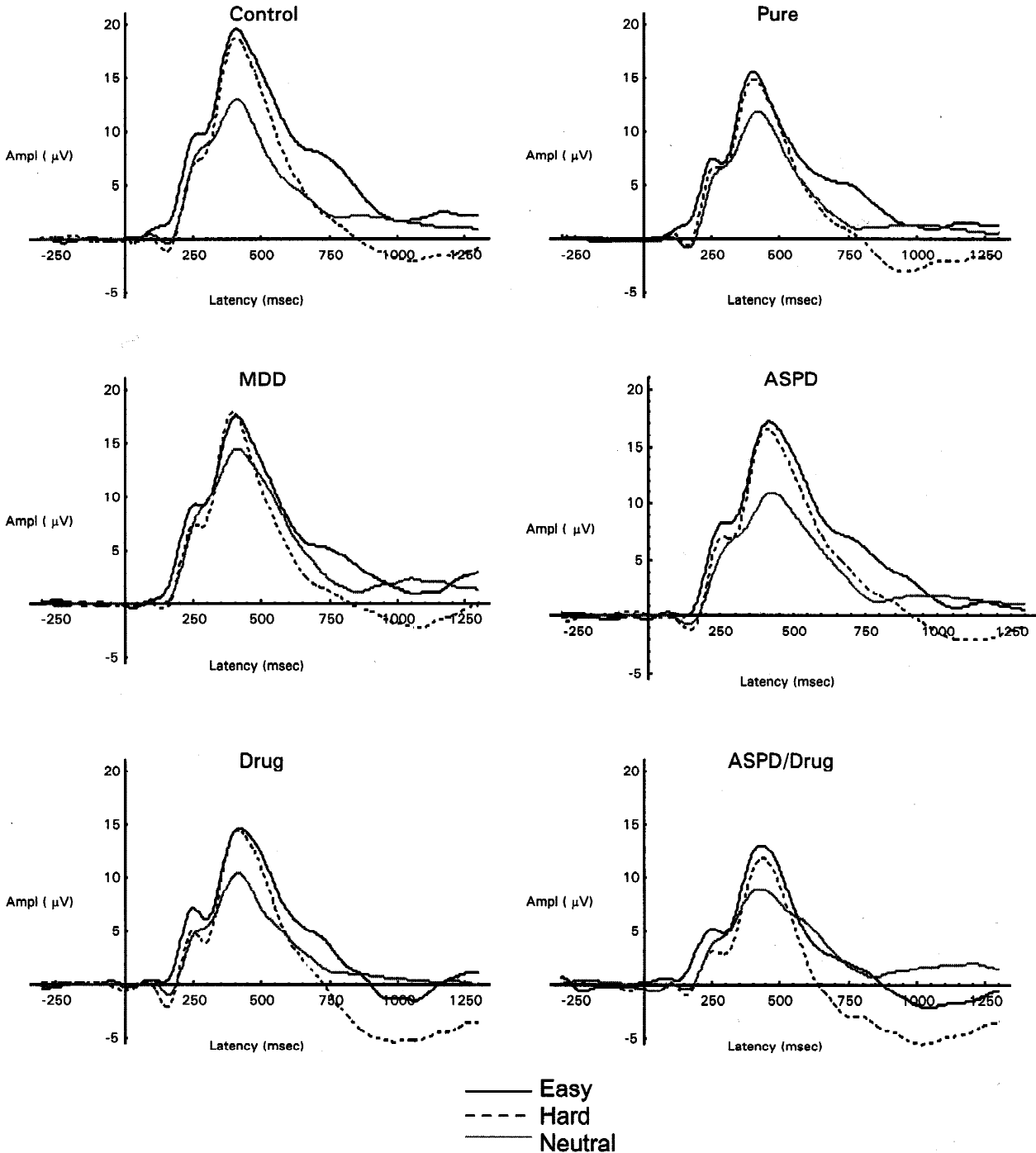


Figure 1. Group grand mean waveforms from Pz. Separate averages are plotted for each of the three conditions.

Table 2. ERP Component Amplitudes and Latencies at Pz

ERP Component	Control	Alcohol group				
		Pure	MDD	ASPD	ASPD/Drug	Drug
Target Condition						
N1 amplitude	-0.94 (3.49)	-0.61 (2.95)	-1.49 (2.68)	-1.29 (2.07)	-1.16 (1.38)	-1.55 (3.42)
N1 latency	156.54 (29.35)	162.11 (32.95)	155.60 (44.53)	143.33 (24.51)	177.08 (63.98)	158.09 (18.19)
P2 amplitude	9.90 (4.99)	7.37 (5.76)	9.43 (6.31)	7.83 (3.33)	6.59 (2.88)	7.16 (4.20)
P2 latency	252.06 (22.63)	244.96 (18.78)	246.55 (43.40)	253.91 (15.61)	249.24 (77.58)	266.36 (13.76)
N2 amplitude	8.19 (5.74)	5.57 (5.68)	7.89 (6.98)	7.51 (3.52)	3.31 (3.64)	5.83 (3.58)
N2 latency	302.45 (22.56)	300.27 (25.60)	309.03 (44.11)	306.34 (22.87)	344.00 (130.27)	305.12 (10.96)
P3 amplitude	20.48 (6.92)	16.43 (5.69)	18.08 (4.97)	17.89 (5.46)	13.26 (3.95)	15.42 (7.21)
P3 latency	412.79 (37.29)	423.83 (47.01)	414.71 (29.85)	429.24 (52.04)	441.84 (41.05)	435.75 (44.37)
Nontarget condition						
N1 amplitude	-1.57 (2.65)	-1.64 (1.73)	-1.62 (3.21)	-1.37 (1.48)	-1.13 (1.93)	-1.51 (2.91)
N1 latency	154.69 (37.42)	165.30 (23.40)	151.69 (30.15)	142.73 (27.79)	171.88 (38.95)	153.78 (31.39)
P2 amplitude	8.89 (4.44)	6.55 (4.05)	7.52 (4.98)	5.57 (3.67)	4.23 (1.49)	6.10 (3.82)
P2 latency	266.07 (41.58)	263.57 (25.73)	251.09 (38.76)	249.10 (40.25)	255.58 (20.03)	255.55 (37.16)
N2 amplitude	7.50 (4.32)	6.44 (4.59)	7.52 (4.88)	5.57 (3.23)	3.99 (1.82)	5.41 (4.90)
N2 latency	321.12 (50.62)	314.67 (31.97)	306.07 (49.00)	302.89 (45.01)	304.13 (18.79)	312.09 (32.91)
P3 amplitude	13.46 (5.39)	12.41 (4.03)	14.47 (5.48)	11.40 (4.21)	9.30 (3.01)	11.09 (4.79)
P3 latency	424.71 (52.67)	427.22 (31.55)	408.42 (64.19)	420.37 (43.40)	421.44 (45.45)	433.39 (60.00)
RT—Easy	913.90 (157.61)	892.16 (145.46)	901.60 (196.69)	1021.69 (167.01)	894.44 (156.17)	976.63 (152.07)
Correct—Easy	39.72 (0.64)	39.68 (0.58)	39.60 (0.74)	39.77 (0.83)	39.67 (1.00)	39.95 (0.23)
RT—Difficult	1186.28 (187.11)	1139.26 (198.90)	1107.07 (242.76)	1340.54 (233.89)	1142.44 (263.36)	1204.00 (222.86)
Correct—Difficult	39.20 (1.07)	39.63 (0.76)	39.40 (1.45)	39.08 (1.80)	39.22 (1.09)	39.26 (0.93)

Note: ERP component amplitudes and latencies at Pz. Means are given, with standard deviations in parentheses. Amplitudes are measured in microvolts; latencies in milliseconds.

responded differentially to the target types and that collapsing them into a single target condition would not be warranted.

As expected, the repeated measures ANOVA of P3 amplitude yielded within-subjects main effects of discrimination difficulty, Pillai's exact $F(1, 109) = 8.69, p = .004, \eta^2 = .074$, with greater P3 amplitude in response to normally oriented heads, presumably reflecting the greater ease of stimulus discrimination required (cf. Verleger, 1988), or subjects' greater confidence in their responses (cf. Ruchkin & Sutton, 1978), and lead, Pillai's exact $F(2, 108) = 107.61, p = .0001, \eta^2 = .666$. There was also a main effect of group, $F(5, 109) = 2.37, p = .044, \eta^2 = .098$. In addition, the effect of lead was conditioned on group membership, Pillai's approximate $F(10, 218) = 2.15, p = .022, \eta^2 = .090$. Despite the main effect of discrimination difficulty, there was no evidence that the different groups responded differentially to the two types of targets: neither the two-way interaction between group and discrimination difficulty, Pillai's exact $F(5, 109) = 0.60$, nor the three-way interaction of group, discrimination difficulty, and lead, Pillai's approximate $F(10, 218) = 0.61$, was significant (both p values less than .70, η^2 less than .030). Moreover, despite the absence of a significant omnibus group \times discrimination difficulty interaction, we examined interaction contrasts comparing amplitudes in response to normal and rotated heads for each alcohol-dependent group relative to the control group. None approached significance (all F ratios less than 2, all p values greater than .15, all η^2 less than .020), confirming that the alcohol-dependent groups did not respond differentially to stimuli differing in ease of discrimination compared with the control group.

A similar analysis of variance, with P3 latency as the dependent measure, failed to produce any significant effects [all F ratios less than 1.60, all p values greater than .15, including the effects most relevant here: group ($\eta^2 = .063$), discrimination difficulty ($\eta^2 =$

.004), the interaction between them ($\eta^2 = .067$), and the three-way interaction with lead ($\eta^2 = .026$)]. As with P3 amplitude, none of the interaction contrasts comparing latencies in the normal and rotated orientation conditions in control subjects versus each affected group was significant, although the control-pure contrast approached significance, $F(1, 109) = 3.56, p = .062, \eta^2 = .067$ (all other F ratios less than 2, p values greater than .15, and η^2 less than .035).

Given these findings, and to simplify the remaining ERP analyses, easy and hard trials were averaged together to create a single "target" condition, with the neutral trials serving as the "nontarget" condition. Each ERP component was thus treated by means of a repeated-measures ANOVA, with group as the between-subjects factor and with condition (target or nontarget) and lead (Pz, P3, or P4) as within-subjects factors. Contrasts on the lead factor examined Pz against the two lateral leads taken together and the left and right parietal leads with each other. We describe only the main effects of group and interactions between group and the within-subjects factors, as these are the only effects that directly address the hypotheses of the paper.

Group Main Effects and Interactions Involving the Group Factor P3 amplitude. There was a significant effect of Group membership on P3 amplitude, $F(5, 109) = 2.46, p = .037, \eta^2 = .101$. Multivariate tests of pairwise contrasts between each group of alcohol-dependent subjects and the control group indicated significant differences in centroids for four of five contrasts: the pure-control contrast, Pillai's exact $F(6, 104) = 3.33, p = .005$; the MDD-control contrast, Pillai's exact $F(6, 104) = 3.05, p = .009$; the drug-control contrast, Pillai's exact $F(6, 104) = 2.89, p = .012$; and the ASPD/drug-control contrast, Pillai's exact $F(6, 104) = 4.01, p = .001$.

Univariate F tests of each dependent measure are analogous to zero-order correlations in multiple regression, yielding the equivalent of validity correlations (Wilkinson, 1975). These were significant when amplitude at Pz, whether in response to target or nontarget stimuli, was the dependent measure, $F(5,109) = 3.04$, $p = .013$ and $F(5,109) = 2.80$, $p = .020$, respectively. There was also a significant F test when amplitude at P4 in response to nontarget stimuli was the dependent measure, $F(5,109) = 2.79$, $p = .020$. These dependent measures thus best discriminate among the different groups (have the least error in relation to the group variable).

The interaction between group and condition was not significant, $F(5,109) = 1.87$, $p = .105$, $\eta^2 = .079$. There was a significant interaction between group and lead, however, Pillai's approximate $F(10,218) = 2.76$, $p = .003$, $\eta^2 = .112$. Follow-up tests indicated that the contrast between midline and lateral leads differed significantly for all five groups of alcohol-dependent subjects compared to control subjects. F ratios, with 1 and 109 df , ranged from 5.37 for the control-ASPD contrast ($p = .022$) to 16.12 for the control-pure contrast ($p = .0001$). Amplitude profiles were flatter across leads in the affected groups than in the control group (Figure 2).

To determine whether the flatter amplitude profiles reflected an overall reduction in strength of the underlying source or differences between affected groups and the control group in the configuration of the underlying source, we repeated this ANOVA after normalizing each individual response vector to unity amplitude (McCarthy & Wood, 1985). The interaction between group and lead was still significant by multivariate test, Pillai's approximate $F(10,218) = 1.91$, $p = .045$, $\eta^2 = .081$, and the contrast between Pz and lateral leads varied as a function of group as well, $F(5,109) = 3.22$, $p = .009$, $\eta^2 = .129$.

When these analyses were repeated for Pz only, a comparable pattern of results emerged. The group effect was significant, $F(5,109) = 3.22$, $p = .009$, but the Group \times Condition interaction was not, Pillai's exact $F(5,109) = 1.90$, $p = .100$. Contrasts on the group factor were again significant for the comparison between control and MDD groups, Pillai's exact $F(2,108) = 3.18$, $p = .045$, control and drug groups, Pillai's exact $F(2,108) = 3.97$, $p = .022$, and control and ASPD/drug groups, Pillai's exact $F(2,108) = 4.93$, $p = .009$. The contrast between control and pure groups was not quite significant, however, Pillai's exact $F(2,108) = 2.69$, $p = .073$.

In summary, there was a significant effect of group membership on P3 amplitude. Amplitude at Pz in both conditions and at P4 in

response to nontarget stimuli best differentiated groups. In all groups of alcohol-dependent subjects, P3 amplitude at the midline was disproportionately reduced relative to the lateral leads, resulting in a flattened amplitude profile. In the MDD group, the altered amplitude profile was due to greater P3 amplitude at the lateral leads, especially P4, than in the control group (Figure 2). In the remaining affected groups, however, P3 amplitude was reduced compared to the control group. The two groups with comorbid drug abuse or dependence, and the ASPD/drug group in particular, had generally reduced mean amplitude across leads.

P3 latency. The groups did not significantly differ with respect to P3 latency, $F(5,109) = 1.44$, n.s., $\eta^2 = .062$. Neither two-way interaction between group and either condition or lead was significant, nor was the three-way interaction among them (all F ratios less than 1.2, all p values greater than .30, and η^2 less than .05). Virtually identical effects of group, condition, and of the Group \times Condition interaction were obtained when we examined latency at Pz only (all F ratios less than 1 and all p values greater than .50).

Early component amplitudes and latencies. We examined amplitude and latency of the N1, P2, and N2 components of the ERP (Table 2). The only significant results involving the group factor were the effect of the Group \times Lead interaction on amplitude of the P2 and N2 components, Pillai's approximate $F(10,200) = 2.35$, $p = .012$, $\eta^2 = .108$, and $F(10,190)^1 = 2.28$, $p = .015$, $\eta^2 = .107$, respectively. For both peaks, contrasts between group and the left-right hemisphere difference were not significant ($\eta^2 = .101$ and .087 for the P2 and N2, respectively). Interaction contrasts between group and the difference in amplitude of the peak between Pz and the lateral leads taken together, however, were significant, $F(5,100) = 2.42$, $p = .040$, $\eta^2 = .108$ for P2 amplitude and $F(5,95) = 2.56$, $p = .032$, $\eta^2 = .127$ for N2 amplitude. For both the P2 and N2, the difference in amplitude between Pz and lateral leads was more pronounced in the control group than in the pure group, the ASPD group, and the ASPD/drug group. The control-MDD contrast was nearly significant for the N2 wave. After individual response vectors had been normalized, the Group \times Lead interaction was still significant for the N2, Pillai's approximate $F(10,190) = 2.51$, $p = .030$, $\eta^2 = .098$, and this was still due to the contrast between midline and lateral leads varying across groups, $F(5,95) = 2.76$, $p = .023$, $\eta^2 = .127$. The Group \times Lead interaction was no longer significant for P2 amplitude after the data had been normalized, Pillai's approximate $F(10,200) = 1.20$, n.s., $\eta^2 = .057$.

None of the main effects of group on amplitude or latency measures was significant (all F ratios less than 1.75 and 1.00, respectively, η^2 less than .040), nor were any of the interactions of group with condition or of group with condition and lead (all F ratios less than 1.50, largest value of η^2 equal to .066). The absence of group main effects and Group \times Condition interaction effects was confirmed by analyses examining Pz only.

P3 Amplitude and Alcohol or Illicit Drug Use

We examined associations between P3 amplitude and measures of alcohol use history (age when first intoxicated, number of lifetime

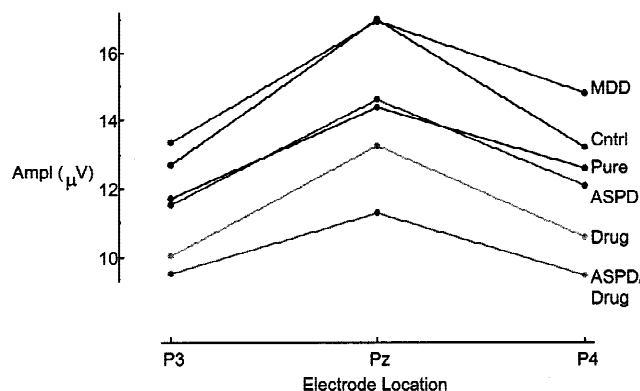


Figure 2. Group mean P3 amplitudes across electrode locations, averaged across conditions.

¹ Because the early components were not always identifiable in all waveforms, the numbers of subjects entering into these analyses, and hence the degrees of freedom associated with various tests, varies for the different components.

intoxications, number of years drinking to the point of intoxication, and maximum consumption in 24 hr) and severity of drinking (MAST analog) by means of within-group correlations with P3 amplitude in response to target stimuli. Age when first intoxicated was recoded for these analyses as the participant's current age if he reported never being intoxicated. Correlations were small in absolute magnitude and none was significant using a criterion of $p = .05$. For the 30 Kendall's τ coefficients, the median absolute magnitude was .10 and only two correlations exceeded .20. Hence, it does not appear likely that alcohol consumption per se accounts for decreased P3 amplitude in the alcohol-dependent groups.

We derived an estimate of alcohol consumption for the 12 months preceding each participant's visit based on the frequency with which participants reported consuming alcohol and the number of drinks consumed per occasion, on average. Within-group correlations with P3 amplitude in response to target stimuli at Pz ranged from $-.11$ (control group) to $.37$ (MDD group) ($Mdn, .10$); none was significant at the .05 level.

With the two groups of subjects with diagnoses of drug abuse or dependence combined (drug group and ASPD/drug group), correlations between the number of lifetime uses of a substance and P3 amplitude at Pz in response to target stimuli ranged from $.03$ to $-.28$. The largest were with lifetime uses of marijuana and of psychedelics; none was significant. In an analysis limited to subjects with cannabis abuse or dependence ($n = 25$), P3 amplitude did not vary as a function of the number of substances abused (one or many), $t(23) = 0.14$, n.s.

Performance Measures

Group differences in average reaction time were not significant (see Table 2), although there was a trend toward significance, $F(5,109) = 2.02$, $p = .081$, $\eta^2 = .085$, with mean reaction times greatest for the ASPD group, especially in response to rotated heads (the hard discrimination condition). Reaction times were significantly longer, on average, when the targets were rotated than when they were normally oriented, $F(1,109) = 284.99$, $p = .0001$, $\eta^2 = .723$. This effect of discrimination difficulty did not vary with group membership, $F(5,109) < 1$, $\eta^2 = .049$. Because average reaction times were positively skewed, we repeated this analysis using a log transformation; the results were virtually identical.

The groups did not differ with respect to response accuracy, $F(5,109) = 0.34$, n.s. There was a small but significant effect of discrimination difficulty, $F(1,99) = 10.60$, $p = .002$, $\eta^2 = .089$. Subjects responded with greater accuracy on easy trials (Table 2). As with the reaction time data, the interaction of discrimination difficulty and group was not significant, $F(5,109) < 1$.

Discussion

In the present study, the amplitude of the P3 wave among adult males performing a visual discrimination task significantly differed between subjects with a lifetime diagnosis of alcohol dependence, irrespective of the presence or absence of any additional psychiatric comorbidity, and a comparison group of subjects drawn from the same epidemiological sample. P3 amplitude was reduced to a greater degree at the midline relative to lateral leads, resulting in a flatter amplitude profile. A flattened profile, although along the midline rather than a sagittal axis, has been reported in other studies of alcoholic men (Hermanutz, Cohen, & Sommer, 1981; Pfefferbaum et al., 1987). Latency of the P3 did not similarly vary across groups. There were no significant main effects of group on the amplitude or latency of any of the early peaks of the ERP

waveform. Amplitude profiles of the N2 and P2, however, were flattened among three of the five alcohol-dependent groups.

Our finding that alcohol dependence among adult men affects P3 amplitude is not a novel one; such subjects typically manifest altered ERP characteristics relative to control-group subjects, at least on relatively challenging tasks such as the task used in the present study, and the most robust effect is diminished amplitude of the P3 wave (e.g., Porjesz & Begleiter, 1996). The primary contribution of the present study is twofold: determining the role of the comorbidity between alcoholism and other disorders in accounting for the reduced amplitude of the P3 commonly observed among alcoholics; and replicating in an epidemiological sample the ERP deficits observed among alcoholic men in other studies using primarily treatment samples.

ERPs in all groups of alcohol-dependent subjects in this study, including those without any comorbid pathology (pure group), differed from ERPs of subjects in the control group. Consistent with the results of other studies (O'Connor et al., 1986; Pfefferbaum et al., 1991; Porjesz & Begleiter, 1996), there was no evidence that alcohol use itself accounted for the altered ERPs of alcoholic subjects, nor was there any evidence that the task used to elicit ERPs was relatively more difficult for alcoholic subjects than for subjects in the control group.

Like subjects with comorbid psychopathology, subjects in the pure group were characterized by a flatter amplitude profile of the P3 across the three electrode locations used in the present study relative to control subjects (Figure 2). Moreover, pure alcoholics resembled antisocial alcoholics in that the amplitude profiles of the P2 and N2 were also flattened in these groups. Altered characteristics of the ERP waveform among pure subjects occurred despite the absence of any additional psychiatric disorder other than alcoholism and despite the fact that the course of alcoholism among these subjects was generally less severe than among subjects with additional disorders (see Table 1). Alcoholism by itself thus appears sufficient to affect P3 amplitude in adult men.

Nevertheless, comorbid drug abuse or dependence was associated with the greatest reductions in P3 amplitude, especially among subjects with comorbid ASPD as well. The difference in mean amplitude at Pz, averaged across target and nontarget stimuli, between the control group and the ASPD/drug group equaled $5.6 \mu\text{V}$, which represents just over one SD (1.04), using the control-group SD as an estimate, conservative in this case, of the population SD (i.e., Glass's Δ ; Rosenthal, 1994). The corresponding estimate of effect size for the contrast between the control group and the drug group at Pz was two-thirds of a SD (mean difference, $3.7 \mu\text{V}$; Glass's Δ , 0.68). Hence, although alterations in ERPs seem to reflect a general characteristic of alcoholic adult men, comorbidity of drug abuse or dependence, perhaps especially when combined with antisocial personality, is associated with the greatest degree of amplitude reduction as well as a sizable effect.

That the interaction between group and the contrast between P3 amplitude at the midline relative to lateral leads was significant after the data had been normalized suggests that alcohol-dependent subjects differed from control subjects with respect to the underlying source configuration giving rise to the P3 (cf. McCarthy & Wood, 1985). That a flattened amplitude profile characterized the ASPD group as well as the other affected groups, despite the absence of a significant control-ASPD contrast, was presumably due to lack of power. Measures of effect size, calculated as described above, tend to bear this out: Glass's Δ was nearly identical for the contrast in amplitude at Pz, averaged across target condi-

tions, between control and pure groups and between control and ASPD groups ($\Delta = 0.47$ and $\Delta = 0.43$, respectively).

The ERPs of subjects with comorbid lifetime depression were especially intriguing. Subjects in this group were similar to subjects in the other groups in that they differed significantly from the control group with respect to their mean P3 amplitude profile. More than with any other group, however, it appeared to be the pattern of responses that differentiated depressed alcoholics from the control group. The flattened amplitude profile in this group was not due to disproportionately reduced amplitudes at the midline but in large measure to these subjects having *greater* mean amplitude of the P3 than control subjects at lateral leads, especially P4.

Univariate tests of the group factor were significant for responses to both target and nontarget stimuli at Pz and for responses to nontarget stimuli at P4. These *F* tests serve as the equivalent of validity coefficients in multiple regression, indicating which response variables best discriminate among groups (Wilkinson, 1975). That these were significant for both stimulus types at Pz is certainly consistent with the flattened amplitude profile observed among all alcohol-dependent groups, which was clearly due to disproportionately reduced amplitude at the midline. That responses to neutral stimuli at P4 also significantly discriminated among groups seems likely due in large part to the greater mean amplitude at P4 among depressed alcoholics relative to control-group subjects (Figure 2). As the right parietal cortex is implicated in directing attention on visual-spatial tasks (Mesulam, 1990), it may be that the task elicited relatively greater visual-spatial attention among subjects with lifetime depression compared with control subjects, which may reflect a tendency toward greater vigilance or even anxious arousal in general.

In addition to examining the effects of comorbidity of other psychiatric disorders with alcoholism on characteristics of the ERP and describing the effects of specific patterns of comorbidity on ERPs, the present study adds to the existing literature in its use of an epidemiological sample. To the best of our knowledge, ERP studies with alcoholic adult men have all used samples of men in treatment or seeking treatment or samples of previously treated abstinent alcoholics. The present study, by contrast, drew from a large, community-based sample broadly representative of middle-aged men in Minnesota, which offers greater generalizability of

findings. Because the degree and type of comorbidity is likely to differ between treatment samples and the general population, this approach is doubly advantageous.

Although the size of the groups in the present study is directly proportional to the number of subjects with different patterns of alcoholism comorbidity in our community-based sample of men, some of the groups are relatively small. This necessitates some caution in making inferences from these data and increases the desirability of replicating the present results. Furthermore, the larger sample from which the present sample was drawn was limited to biological fathers and stepfathers of twin sons, the majority of whom were married or had previously been married. Thus, men who had not married or had not had children were not eligible, and the results obtained here may not generalize to such individuals.

Despite these shortcomings, by specifically addressing the presence or absence of comorbidity of other psychiatric disorders among alcoholic men, as well as subtyping them by comorbidity, the present study indicates that alcoholism by itself is associated with altered ERP characteristics. This pattern of results suggests that reduced amplitude of the P3 may reflect a psychophysiological dimension underlying a spectrum of related psychopathology, including alcohol dependence, other substance use disorders, and antisocial personality (Iacono, 1998). Nevertheless, subjects with the greatest degree of such pathology—antisocial personality disordered alcoholic men with a comorbid diagnosis of illicit drug abuse or dependence—had the smallest mean amplitudes.

In contrast, subjects with a lifetime diagnosis of major depression in addition to alcohol dependence did not have uniformly reduced amplitude ERPs relative to control subjects. In fact, this group appeared to differ from the control group primarily with respect to the pattern of responses. Future research will undoubtedly help elucidate any differences between internalizing and externalizing disorders with respect to effects on the P3. Thus, grouping subjects by patterns of comorbidity revealed some differences among them in the specific nature of alterations of ERP characteristics relative to control-group subjects. These patterns, although subtle, may, if replicated, help shed light on the etiology of different types of alcoholism and, to the degree that P3 amplitude is a marker of risk, help indicate what type of risk is being “marked.”

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