

P300 amplitude in adolescent twins discordant and concordant for alcohol use disorders

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Abstract

The sons of alcoholics have repeatedly been found to have reduced P300 amplitude. Further, quantitative behavioral genetic and molecular genetic studies indicating a genetic influence on P300 amplitude have fueled speculation that this component may be a biological vulnerability marker for alcoholism. To further explore this possibility, we examined P300 in adolescent twin pairs from an epidemiological sample who were (a) discordant for alcohol abuse/dependence, (b) concordant for alcohol abuse/dependence, or (c) concordant for the absence of alcohol abuse/dependence and other relevant disorders. For discordant pairs, the alcohol abusing/dependent twins' amplitude did not differ from that of non-alcoholic co-twins. Pairs free of psychopathology had greater amplitudes than both alcoholism discordant and concordant pairs. P300 amplitude was more similar in monozygotic than dizygotic discordant pairs, suggesting a genetic influence on P300 amplitude in this group. The findings are consistent with P300 amplitude being a marker of vulnerability to alcohol use disorders. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: P300 amplitude; Alcohol abuse/dependence; Discordant twins; Biological markers; Endophenotype

1. Introduction

Alcoholism is a heterogeneous disorder that appears to be under partial genetic influence (see McGue, 1999, for a review). Having markers of genetic vulnerability would greatly facilitate the study of etiological processes by allowing for the

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identification of those with a genetic vulnerability who have not expressed the disorder, and selection of affected subjects who are more homogeneous in terms of their vulnerability factors. A highly promising candidate marker of risk for alcoholism is the P300 amplitude of the electrocortical event-related potential (ERP) as elicited in a number of tasks (Begleiter and Porjesz, 1988, 1999; Iacono, 1998; van der Stelt, 1999). ERPs are the average electrocortical activity time-locked to either a stimulus or response event. The P300 component of the ERP has been heavily studied in relation to attentional and memory processes (for an overview of ERPs and P300 see Fabiani et al., 2000).

Meta-analysis of a decade's worth of studies (Polich et al., 1994) supported the general finding that the sons of alcoholic fathers have reduced P300 amplitude as elicited by a variety of tasks when compared to the sons of non-alcoholics. The effect was greater with difficult tasks involving visual, rather than auditory stimuli, with subjects under age 17, and for subjects whose fathers had undergone treatment for alcoholism. In addition to a paternal risk effect, the sons of alcoholic mothers have also been shown to have reduced P300 amplitude (Hill et al., 1995a). The parental risk effect is seen in high-risk children who have not yet been exposed to the potentially neurotoxic effects of alcohol (e.g. Begleiter et al., 1984). Even in adult alcoholics, P300 amplitude reduction may be related to a family history of alcoholism rather than to personal alcohol abuse or consumption history (Cohen et al., 1995; Pfefferbaum et al., 1991). In addition to high-risk status being associated with reduced P300 amplitude, adolescents selected from a representative community sample for having small P300 amplitude have higher rates of alcohol abuse/dependence, illicit drug dependence, and related externalizing psychopathology when compared to those with large P300 amplitudes (Carlson et al., 1999), further supporting the sensitivity of reduced P300 as a marker of risk. Perhaps the most compelling evidence for reduced P300 amplitude being an index of risk are findings that small amplitudes predict the development of future substance use and abuse (Berman et al., 1993; Hill et al., 2000; Iacono et al., 2002).

P300 amplitude reduction in those at risk is often interpreted as an indicator of genetic liability for alcoholism or substance use disorder more broadly defined and may qualify as an endophenotype for substance use disorders (Begleiter and Porjesz, 1999; Iacono, 1998). Consistent with this interpretation is the finding that P300 amplitude is genetically influenced. Studies contrasting the similarity between identical, or monozygotic (MZ), twins who share 100% of their genes to that of fraternal, or dizygotic (DZ), twins who share on average 50% of their genes, suggest significant genetic influences on P300 amplitude (but see Rogers and Deary, 1991). O'Connor et al. (1994b) found greater similarity in P300 amplitude elicited by auditory stimuli between MZ than between DZ twin pairs. Biometrical model fitting of the MZ and DZ variances and covariances suggested that the proportion of the total variability in amplitude due to genetic variance (i.e. the heritability or h^2) ranged between 0.41 and 0.60. Katsanis et al. (1997) used a difficult, visual task to elicit P300 and found that genetic variance contributed to about 80% of the individual differences in amplitude, the remainder being attributable to environmental influences that make members of the same family different (i.e. the non-

shared environment or e^2). van Beijsterveldt et al. (2001) also found significant familial similarity in P300 amplitude between members of adolescent twin pairs. Genetic influences (h^2) accounted for family resemblance between male twins, but shared environmental (c^2) influences appeared to be responsible for the similarity between female pairs.

Genetic influences in the general population do not necessarily indicate that P300 amplitude reductions in high-risk groups are influenced by genetic factors. Environmental factors associated with being in a high risk family (including increased probability of being exposed to the deleterious effects of alcohol and other substances of abuse) could have a predominant influence on variation among these vulnerable individuals and be responsible for reductions in mean amplitude. Estimates from a large family study with subjects from pedigrees with a high density of alcoholism suggest that P300 is moderately heritable in high-risk families (h^2 ranged between 0.30 and 0.53 for a visual oddball task, 0.28 and 0.40 for an auditory oddball task (Almasy et al., 1999); and 0.09 and 0.54 for a semantic priming task (Almasy et al., 2001)). In contrast, Polich and Bloom (1999) reported significant within family similarity for visual, but not auditory, P300 amplitude in families at high risk for alcoholism. Further and perhaps most intriguingly, model-fitting of variance in P300 amplitude among different types of kinships suggested that factors transmitted from parents to offspring have a greater impact on amplitude for high-risk families than for low-risk families (Hill et al., 1999c).

These findings from high-risk families are consistent with both genetic and non-shared environmental influences playing contributory roles in P300 amplitude in individuals with a familial vulnerability for alcoholism. Differences among family members in involvement with alcohol or other psychoactive substances could be a source of non-shared environmental influence reducing P300 amplitude. For example, individuals with an alcohol use disorder may have reduced P300 amplitude largely because of the negative consequences of excessive alcohol consumption. If so, one would expect that twin pairs in which one member has a diagnosis of alcohol abuse or dependence and the other does not would differ in their P300 amplitudes. On the other hand, the finding of comparable low amplitudes in both members of such discordant pairs would be consistent with a familial risk factor influencing both P300 amplitude and alcoholism. If, in addition, the members of discordant MZ pairs were significantly similar to each other in P300 amplitude despite differences in substance pathology, and were more similar than members of DZ pairs, then genetic influences on this risk factor would be implicated.

In the current report, adolescent twin pairs from a large, population-based study were identified as being discordant for alcohol use disorder, concordant for alcohol use disorder, or free of these and related forms of psychopathology. The P300 amplitudes from members of discordant pairs with an alcohol use disorder were compared to those of their co-twins without alcohol abuse/dependence to ascertain if there was a systematic effect of alcoholism on P300 amplitude in adolescence. These late adolescent young men and women were at an age in which alcohol abuse begins to be manifested, but still close to the age at which P300 amplitude differences between high and low risk subjects are most robust (Polich et al., 1994). We used a

difficult discrimination task employing visual stimuli based on the “rotated heads” oddball paradigm of [Begleiter et al. \(1984\)](#) to elicit the P300. Since it is possible for members of the same twin pair to differ in alcohol use disorder diagnosis but not in many aspects of their actual substance use, a lack of differences between cotwins’ P300 amplitude may be due to comparable exposure to substances of abuse. For this reason, the alcohol disorder affected and unaffected members of the discordant pairs were also compared on several substance use measures. Further, several disorders commonly co-occurring with alcohol abuse/dependence in adolescence have been associated with reduced P300 amplitude ([Iacono et al., 2002](#)) including conduct disorder (CD) ([Bauer, 1997](#); [Bauer and Hesselbrock, 1999a,b](#)), oppositional defiant disorder (ODD), attention-deficit/hyperactivity disorder (ADHD) ([Klorman, 1991](#)), drug abuse/dependence ([Biggins et al., 1997](#); [Branchey et al., 1993](#)), and nicotine dependence ([Anokhin et al., 2000](#)). In fact, [Bauer and Hesselbrock \(1999a,b\)](#) found reduced P300 amplitude in adolescents with more than the median number of CD symptoms for their gender, but did not find differences based on a family history of alcoholism or other types of substance dependence. Factor analysis of phenotypic covariance across alcohol abuse/dependence, many of these other disorders, and anxiety and mood disorders suggests that antisocial, alcohol and drug disorders primarily load together on a common latent externalizing factor while anxiety and mood disorders primarily load on an internalizing factor ([Kendler et al., 1997](#); [Krueger, 1999](#); [Krueger et al., 2001](#)). Two recent independent twin studies suggest that the majority of the variance (over 80%) in this latent externalizing phenotype was due to genetic factors ([Krueger et al., 2002](#); [Young et al., 2000](#)). Because of the association between alcohol use disorders and externalizing psychopathology and the previously reported relations between reduced P300 and other disorders associated with alcoholism, prevalence rates for these other disorders were provided for the affected and unaffected members of discordant twin pairs. A lack of a difference in amplitude between members of discordant pairs may be due to similarity in these other disorders.

Discordant pairs were compared to concordant pairs to determine if their P300 amplitudes were similar. In order to determine if the discordant and concordant pairs had reduced P300 amplitude, they were both also compared to the diagnosis-free twin pairs. Further, to determine if P300 in discordant pairs could be genetically influenced the similarity in P300 amplitude between members of MZ twin pairs was compared to that of DZ pairs.

Support for P300 as a biological marker for alcoholism in both males and females has been mixed. The majority of studies reporting significant differences between those with and without first-degree alcoholic relatives have involved the sons or brothers of male alcoholics. The effect of a family history of alcoholism on P300 amplitude may differ for males and females, with greater differences observed between high and low-risk males than between high and low-risk females using both visual ([Hill and Steinhauer, 1993](#)) and auditory ([Hill et al., 1995a](#); [Steinhauer and Hill, 1993](#)) tasks. [van der Stelt et al. \(1998\)](#), however, found comparably reduced P300 amplitude in both high-risk boys and girls with a visual task, and in the children of both alcoholic mothers and fathers. Because of the controversial nature

of the possible interactions between sex and alcoholism risk, we assessed sex effects in our analyses.

Consistent with evidence supporting P300 as a risk marker, we predicted that P300 amplitude would not differ between the discordant pair members with and without alcohol abuse/dependence. Further, we predicted that the lack of amplitude differences would not be mirrored by comparable levels of substance use in the alcoholic and non-alcoholic members of the discordant twin pairs. We also predicted that members of discordant pairs would have significantly smaller P300 amplitude than diagnosis-free twin pairs, but would have amplitudes comparable to concordant pairs. Finally, we anticipated that P300 amplitude in discordant twins would show greater within pair similarity for the genetically more similar MZ pairs than for the DZ twins consistent with a significant genetic influence on P300 amplitude in these high-risk adolescents. Although the discordant twin approach has been used to examine P300 amplitude as a putative marker in other forms of psychopathology (Weisbrod et al., 1999), to the best of our knowledge this is the first study to examine P300 amplitude in twins discordant for alcohol use disorders.

2. Method

2.1. Participants

Two hundred seventy two young men and 394 young women participated in this study. Participants came from the Minnesota Twin Family Study (MTFS), a longitudinal investigation of genetic and environmental contributions to the development of substance use disorders and related psychopathology. Details regarding the recruitment strategy and general aims of the MTFS were provided by Iacono et al. (1999). In short, the twin pairs in this study were identified from birth certificates and recruited to participate in this study between the ages of 16 and 18 (mean age = 16.93 years, SD = 0.57.) Over 95% of the subjects in the MTFS were Caucasian, which is representative of the state of Minnesota at the time of their births. The adolescent males constituted 42 pairs of male twins discordant for alcohol abuse/dependence (26 MZ pairs, 16 DZ pairs), 20 pairs of concordant male twins (14 MZ pairs, 6 DZ pairs), and 74 pairs of diagnosis-free male twins (55 MZ pairs, 19 DZ pairs). The female subjects were distributed as follows: 30 pairs of discordant twins (16 MZ pairs, 14 DZ pairs), 19 pairs of concordant twins (14 MZ pairs, 5 DZ pairs), and 148 pairs of diagnosis-free twins (101 MZ pairs, 47 DZ pairs). These constituted all intact twin pairs in these groupings with valid P300 data.

Zygoty was determined by comparison of three estimates of twin similarity: (1) a questionnaire assessing the parents' rating of twin similarity, (2) an experienced staff member's assessment of physical similarity, and (3) an algorithm based on the cephalic index, ponderal index, and a count of fingerprint ridges. If there was disagreement among these estimates, blood was drawn for serological evaluation. The validity of this approach was supported by an analysis of 50 twin pairs that

showed that when all three measures of similarity were in agreement, the resulting zygosity determination was always confirmed by the blood test.

2.2. Procedure

The ERP data were collected during a 3.5-h psychophysiological protocol in the morning of the participants' visit to our laboratories. In the afternoon of their visit, the twins were separately administered structured clinical interviews by trained master's and bachelor's degree interviewers. Members of twin pairs were assessed simultaneously with the same procedures in parallel laboratories by staff who had no knowledge of co-twin status.

2.2.1. Diagnostic assessment

The classification system in place at the initiation of the study was the Diagnostic and Statistical Manual of Mental Disorders, third ed., revised (DSM-III-R: [American Psychiatric Association, 1987](#)) and its diagnostic criteria were used in this study. Participants were interviewed about current and past symptoms of alcohol abuse and dependence, nicotine dependence, and street drug abuse and dependence using the Substance Abuse Module (SAM) of the Composite International Diagnostic Interview (CIDI: [Robins et al., 1987, 1988](#)). In addition to symptoms of substance use disorders, aspects of substance use were also covered with the SAM. The street drugs assessed included amphetamines, cannabis, cocaine, hallucinogens, inhalants, opiates, phencyclidine, and sedatives. The mothers of the twins were also interviewed regarding their offsprings substance abuse/dependence using the Diagnostic Interview for Children and Adolescents, Parent version (DICA-P: [Reich, 2000](#)). Externalizing psychopathology was also assessed. Adolescents were interviewed regarding ADHD and ODD with the child and adolescent version of the DICA. CD was assessed with an interview developed by the MTFs to cover all criteria of CD and adult symptoms of antisocial personality disorder ([Holdcraft et al., 1998](#)). Mothers were interviewed about their children's ADHD, ODD, and CD symptoms using the DICA-P.

Teams of graduate students with advanced training in the diagnosis of psychopathology conducted case conferences in which they reviewed each structured interview. A tape recording of the interview was consulted in ambiguous cases, and symptoms were assigned only when the team reached consensus. A computer algorithm was used to (a) combine data from the adolescents' and mothers' reports, and (b) assign DSM-III-R diagnoses. A symptom was considered present if it was endorsed by either the mother or the adolescent using a "best estimate" approach ([Leckman et al., 1982](#)). This procedure resulted in adequate diagnostic reliability: Cohen's kappa ranged from 0.71 for ODD to over 0.91 for all of the substance use disorders. Lifetime diagnoses were assigned at the definite (at a minimum all required symptoms were present) or probable (all but one symptom present) levels of certainty. Due to (a) the somewhat arbitrary nature of the cut off points for the necessary number of symptoms to meet criteria for a disorder and (b) the nature of the comparisons to be made in this study between twins with and without a disorder,

we considered a disorder to be present if it was met at the definite or probable level. Otherwise, it was considered absent.

Twin pairs were considered to be discordant if one member had a diagnosis of alcohol abuse or dependence and the other member was without either an abuse or dependence diagnosis. In concordant pairs, both members had an alcohol abuse or dependence diagnosis. The diagnoses-free comparison twins were pairs selected to be at low risk for alcohol disorders. As such, neither member had a diagnosis of alcohol abuse/dependence or the related disorders of street drug abuse/dependence, nicotine dependence, CD, ADHD, or ODD.

2.2.2. *Psychophysiological assessment*

Each twin sat in a high backed, padded chair in identically configured, darkened laboratory rooms. An electrode cap was used to collect electroencephalographic (EEG) signals from the Pz, P3, and P4 scalp sites. EEG electrodes were referenced to linked earlobes. Ag–AgCl electrodes were placed above the pupil and near the outer canthus of one eye in order to record electrooculographic (EOG) signals. A ground electrode was placed on the right shin. EEG and reference site impedance was below 5 K Ω . EOG and ground site impedance was kept below 10 K Ω . Data were digitally sampled at a rate of 256 samples/s over a 2000 ms epoch with a 500 ms pre-stimulus baseline. A Grass Model 12A Neurodata acquisition system was used to amplify and filter the EEG. These signals were amplified 20 000 \times and were filtered within a window defined by 1/2 amplitude low and high frequency filter settings at 0.01 Hz and 30 Hz.

2.2.3. *Rotated heads task*

The visual, oddball paradigm used to elicit the ERPs was based on the “rotated heads task” of Begleiter et al. (1984). There were five types of stimuli representing different versions of an aerial view of a cartoon head. The target stimuli consisted of an oval with a nose and a single ear drawn in. Non-target trials consisted of a simple oval with no nose or ear. Participants were instructed to respond to targets by pressing the button on the arm of their chair corresponding to the side of the head the ear was on. They were not to make a response to the non-targets. On half of the target trials the nose was pointed up and, thus, the side of the head the ear was on matched the side of the chair requiring the response (i.e. ears on the left side of the head required a press of the left button, ears on the right side required a right-hand button press.) For the other half of the target trials, the nose was pointed down and now the side of the screen the ear was on required a response from the hand on the opposite side of the participant’s body. Ears on the left side of the screen were now on the right side of the head and therefore required a press of the right button. Conversely, ears on the right side of the screen now required a left hand button press, because the ear was on the left side of the head.

The stimuli were presented on a computer monitor positioned approximately 48 cm in front of the participants. There were 160 nontarget trials, and 40 difficult (head

with nose pointed down) and 40 easy (head with nose pointed up) trials. Stimuli were presented in pseudorandom order for 98 ms each with a random interstimulus interval ranging between 1 and 2 s. Clipping of the EEG or EOG signal caused rejection and repetition of a trial. Participants completed practice trials until they comprehended the task instructions. They were told to respond accurately but as fast as possible.

2.2.4. ERP processing

The data were processed in two ways prior to averaging in order to reduce the effects of noise. First, the effect of blinks and other ocular artifacts on the EEG was reduced by using the blink correction method of Gratton et al. (1983). Second, a 7.5 Hz lowpass digital filter was used to reduce high frequency noise not eliminated by the Grass filters.

EEG was averaged within task conditions to provide ERPs. The ERPs analyzed in this study come from the average across all target conditions. To our knowledge no significant interaction between alcoholism risk groups and target condition has been reported using the rotated heads task. High risk subjects have repeatedly been reported to have smaller P300 amplitudes than low risk subjects in both the “easy” and “hard” target conditions described here (Begleiter et al., 1984; Hill and Steinhauer, 1993; O’Connor et al., 1994a, 1986, 1987; —but see Hill et al., 1995a). Given the lack of a reliable interaction between the two target conditions and risk status, some investigators have chosen to analyze only one condition (Hill et al., 1999a,b). We have chosen to analyze the waveforms averaged across target conditions because (a) as noted, there is little to no evidence of an interaction between target condition in the rotated heads task and risk group in the extant literature, (b) given the lack of such an interaction averaging both target conditions should increase the reliability of our measures by doubling the number of trials contributing to the waveform averages, and (c) we wish to ease the exposition of the results.

A computer algorithm identified the largest peak amplitude occurring between 200 and 800 ms following stimulus onset. A rater blind to participants’ diagnoses compared the waveform at Pz to those recorded at P3 and P4 in order to confirm the selected peaks for the mean target waveforms. Misidentified peaks were corrected. In cases where there was more than one peak of comparable amplitude, the second peak was chosen in order to reduce the probability that P200 was misidentified as the P300. Latency was defined as the difference in milliseconds between stimulus onset and the peak of the P300 component. Pz was chosen as the site for analysis because it has frequently been the site of focus or special attention in studies of alcohol use disorder risk and P300 amplitude (Begleiter et al., 1987; Hill et al., 1995a,b,c; Hill and Steinhauer, 1993; Hill et al., 1988; Polich et al., 1988; Porjesz and Begleiter, 1990; Steinhauer and Hill, 1993; Steinhauer et al., 1987; Whipple et al., 1991).

3. Results

3.1. *Effect of an alcohol use disorder on P300 in discordant pairs*

Descriptive statistics for P300 amplitude, P300 latency, reaction time and task error rate in the discordant pairs are presented in [Table 1](#). Further, grand average ERP waveforms are presented in [Fig. 1](#). To assess the effect of alcohol abuse or dependence on the amplitude of the P300 component, a repeated measures ANOVA with the diagnostic status of the discordant pair members as a single within-pairs factor with two levels (alcohol abuse/dependence present, no alcohol abuse/dependence) and sex as a between-subjects factor with two levels (male, female) was conducted. Adolescents without an alcohol use disorder did not differ significantly in their P300 amplitude from their co-twins with such a diagnosis [$F(1, 70) = 0.015, P = 0.904$]. Further, the sex of the twin pair did not significantly interact with diagnostic status to influence P300 amplitude [$F(1, 70) = 0.016, P = 0.901$]. Females, however, did have significantly greater P300 amplitude than males [$F(1, 70) = 10.274, P = 0.002$]. Repeated-measures ANOVAs with the same design were conducted with P300 latency, reaction time, and task performance error data as well. There were no significant within-pairs or between-subjects main or interaction effects for either latency or reaction time. There was no significant within-pair effect for error rate [$F(1, 70) = 0.456, P = 0.501$], but females made significantly more errors than did males [$F(1, 70) = 8.007, P = 0.006$]. Sex and alcohol disorder status did not interact significantly to influence error rate [$F(1, 70) = 0.758, P = 0.226$].

3.2. *Differences in substance use and psychopathology between members of discordant pairs*

It is possible that a lack of a significant difference between the affected and unaffected members of discordant pairs may be due to similarities in substance consumption or rates of comorbid psychopathology. Several quantitative measures of substance involvement derived from the SAM were compared across discordant twin pair members with and without alcohol abuse/dependence. In particular the amount of alcohol consumed in the previous year, the number of years since the first drink, maximum amount of alcohol consumed on one occasion, the amount of tobacco used per month, and the number of uses of street drugs were compared. Due to subject refusal or data coding errors, some participants were missing information as follows: estimated alcohol consumption (two males), maximum alcohol consumption (two males), years since first drink (one male), number of street drug uses (two males), and tobacco consumption (one male). Because these measures were positively skewed in this adolescent population, a non-parametric test, the Wilcoxon Signed Ranks Test, was used to compare affected and unaffected members of discordant pairs separately by gender. Descriptive statistics for these substance use measures in the discordant pairs are provided in [Table 2](#). The males with alcohol abuse or dependence had consumed more drinks in the previous year [$Z = 4.086, P < 0.001$], started drinking at a younger age [$Z = 3.644, P < 0.001$], and consumed

Table 1
P300 amplitude, P300 latency, manual reaction time, and number of target errors for discordant, concordant, and diagnosis free twin pairs

Variable	Discordant pairs			Concordant pairs			Diagnosis-free pairs			
	<i>N</i>	Alc., mean (SD)	No-Alc., mean (SD)	<i>N</i>	Twin 1, mean (SD)	Twin 2, mean (SD)	<i>N</i>	Twin 1, mean (SD)	Twin 2, mean (SD)	
<i>P300 amplitude (microvolts)</i>										
Male	MZ	26	22.66 (6.84)	21.58 (7.59)	14	20.21 (6.46)	21.62 (7.40)	55	25.09 (9.06)	25.60 (8.57)
	DZ	16	19.28 (3.15)	21.06 (6.90)	6	22.18 (6.28)	27.10 (9.20)	19	27.73 (8.28)	24.66 (7.07)
	Total	42	21.37 (5.91)	21.37 (7.25)	20	20.80 (6.31)	23.27 (8.15)	74	25.77 (8.88)	25.36 (8.17)
Female	MZ	16	28.32 (8.83)	29.14 (9.96)	14	26.14 (10.45)	25.69 (7.41)	101	26.77 (8.95)	26.29 (8.37)
	DZ	14	25.66 (9.00)	22.98 (5.45)	5	25.86 (3.81)	24.91 (6.47)	47	29.49 (9.04)	26.66 (8.01)
	Total	30	26.02 (8.76)	26.27 (8.63)	19	26.07 (9.06)	25.49 (7.01)	148	27.64 (9.04)	26.41 (8.23)
<i>P300 latency (milliseconds)</i>										
Male	MZ	26	434.20 (54.93)	445.76 (42.12)	14	450.34 (60.58)	450.61 (60.72)	55	446.31 (50.92)	449.01 (58.43)
	DZ	16	434.33 (72.03)	464.84 (53.88)	6	452.48 (57.00)	416.67 (61.25)	19	472.86 (57.62)	456.83 (61.91)
	Total	42	434.25 (61.14)	453.03 (47.24)	20	450.98 (58.03)	440.43 (61.36)	74	453.13 (53.60)	451.01 (59.01)
Female	MZ	16	433.84 (47.51)	444.58 (37.42)	14	432.20 (53.57)	440.29 (68.77)	101	428.99 (50.14)	432.24 (51.51)
	DZ	14	445.03 (46.13)	450.33 (64.01)	5	442.19 (52.22)	506.25 (73.16)	47	441.57 (50.41)	444.48 (60.96)
	Total	30	439.06 (46.41)	447.27 (50.69)	19	434.83 (51.95)	457.65 (74.13)	148	432.99 (50.40)	436.13 (54.78)
<i>Reaction time (milliseconds)</i>										
Male	MZ	26	967.81 (200.09)	1005.60 (166.71)	14	1060.21 (176.27)	1047.04 (172.43)	53	1023.53 (155.43)	1027.79 (149.44)
	DZ	16	1119.84 (226.42)	1064.31 (143.39)	6	962.75 (209.70)	873.25 (120.65)	19	1003.76 (170.58)	1009.63 (133.61)
	Total	42	1025.73 (220.80)	1027.96 (159.06)	20	1030.98 (186.90)	994.90 (175.64)	72	1018.31 (158.58)	1023.00 (144.73)
Female	MZ	16	1033.44 (170.10)	1062.84 (149.57)	14	1066.25 (235.16)	1094.11 (207.98)	101	980.47 (163.66)	975.72 (155.01)
	DZ	14	1004.25 (133.46)	1000.47 (167.75)	5	1004.00 (228.98)	1025.70 (113.18)	46	996.81 (190.53)	991.18 (164.36)
	Total	30	1019.82 (152.21)	1033.73 (158.71)	19	1049.87 (228.88)	1076.11 (187.20)	147	985.58 (172.02)	980.56 (157.59)
<i>Number of target errors</i>										
Male	MZ	26	1.04 (1.15)	0.96 (1.11)	14	1.07 (1.07)	2.21 (2.36)	53	1.19 (1.82)	1.06 (1.43)
	DZ	16	1.44 (1.55)	1.75 (2.54)	6	1.67 (0.75)	0.50 (0.55)	19	1.63 (2.03)	0.95 (1.39)
	Total	42	1.19 (1.31)	1.26 (1.81)	20	1.10 (0.97)	1.70 (2.13)	72	1.31 (1.87)	1.03 (1.41)
Female	MZ	16	2.19 (2.29)	1.25 (1.18)	14	5.00 (5.67)	2.50 (2.95)	101	2.80 (6.96)	2.17 (2.60)
	DZ	14	3.86 (4.90)	3.71 (4.78)	5	0.80 (0.84)	1.60 (1.52)	46	2.67 (3.25)	2.15 (2.38)
	Total	30	2.97 (3.76)	2.40 (3.54)	19	3.89 (5.20)	2.26 (2.64)	147	2.76 (6.04)	2.16 (2.53)

Note: One member of each concordant and diagnosis-free twin pair was randomly assigned to Twin 1 or Twin 2 status, the co-twin receiving the converse assignment. Reaction time and error rate data were missing for members of three twin pairs due to computer failure in data storage. *N* = number of twin pairs.

more alcohol in 24 h [$Z = 3.106$, $P = 0.002$] than their co-twins who do not have an alcohol use disorder diagnosis. The affected members of these discordant pairs also had used more tobacco in a typical month [$Z = 2.498$, $P = 0.012$] and street drugs significantly more times [$Z = 2.126$, $P = 0.033$] than their cotwins. Female twins with an alcohol use disorder also drank more in the previous 12 months [$Z = 2.629$, $P = 0.009$], and had drunk more in 24 h [$Z = 3.592$, $P < 0.001$] than their co-twins. The female twins with an alcohol disorder also had used street drugs significantly more times than their co-twins without a diagnosis [$Z = 2.744$, $P = 0.006$]. They, however, did not differ significantly from their co-twins in the number of years since their first drink [$Z = 1.691$, $P = 0.091$] or the amount of tobacco smoked in the previous month [$Z = 1.719$, $P = 0.086$].

To assess the possibility that years since first drink or tobacco consumption were systematically related to P300 amplitude and thus contributed to the lack of P300 amplitude differences between alcoholic and nonalcoholic twins, we computed nonparametric correlation coefficients (Kendall's τ) between these variables and amplitude. For the male adolescents with an alcohol use disorder, there was no relationship between P300 and years since first drink [$\tau(41) = 0.131$, $P = 0.260$] or tobacco consumption [$\tau(41) = 0.130$, $P = 0.245$]. P300 was also not related to years since first drink [$\tau(41) = -0.086$, $P = 0.466$] or tobacco consumption [$\tau(41) = 0.053$, $P = 0.642$] in their co-twins. Similarly, for the female discordant twins there was no significant relationship between P300 amplitude and years since first drink [affected twins: $\tau(30) = -0.024$, $P = 0.867$; unaffected twins: $\tau(30) = -0.010$, $P = 0.941$] or tobacco consumption [affected twins: $\tau(30) = -0.122$, $P = 0.358$; unaffected twins: $\tau(29) = -0.102$, $P = 0.466$].

P300 amplitude may be reduced in both members of a discordant pair due to concordance for some other condition related to both alcoholism and P300 amplitude. Rates of street drug abuse/dependence, nicotine dependence, and externalizing disorders were evaluated in the members of discordant pairs. The number and percent of affected and unaffected members of the alcohol disorder discordant pairs are provided in Table 3. Fisher's exact test was used to determine if a given disorder occurred in a higher percentage of the participants with an alcohol use disorder than in their co-twins without that diagnosis. For males a higher percentage of the alcoholic members of the twin pairs had CD ($P = 0.026$). They did not, however, differ in rates of ODD ($P = 1.000$), ADHD ($P = 0.380$), street drug abuse/dependence ($P = 0.350$), or nicotine dependence ($P = 0.098$). A significantly greater percentage of the female twins with an alcohol disorder also had street drug abuse/dependence ($P = 0.010$) than their cotwins. They did not differ significantly in their rates of CD ($P = 0.072$), ODD ($P = 0.299$), ADHD ($P = 0.237$), or nicotine dependence ($P = 0.435$).

3.3. P300 differences between discordant, concordant, and diagnosis-free twin pairs

Even though the affected and unaffected members of discordant twin pairs had similar P300 amplitudes, the possibility remained that neither type of twin differed in amplitude from adolescents without relevant psychopathology. In other words, these

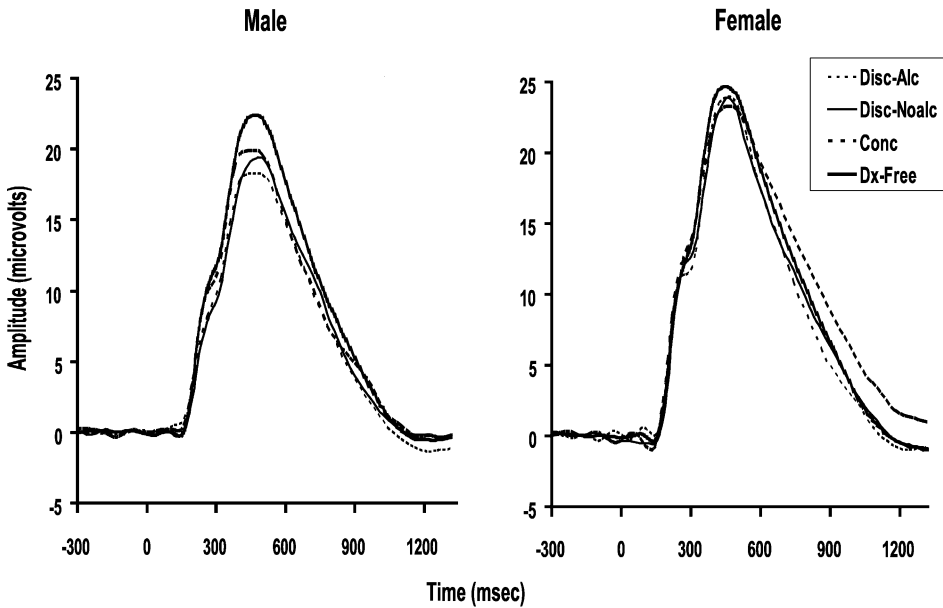


Fig. 1. ERP grand averages for target stimuli at the Pz scalp site are presented separately by sex for adolescent twin pairs discordant for alcohol abuse/dependence (n_{pairs} : male = 42, female = 30), concordant for alcohol abuse/dependence (n_{pairs} : male = 20, female = 19), and concordant for the absence of alcohol abuse/dependence and other relevant disorders (n_{pairs} : male = 74, female = 148). Both members of concordant and diagnosis-free pairs contribute to their respective grand averages. Disc-Alc = member of discordant pair with alcohol abuse/dependence. Disc-Noalc = member of discordant pair without alcohol abuse/dependence. Conc = pairs concordant for alcohol abuse/dependence. Dx-Free = pairs free of diagnoses.

twin pairs may not have reduced P300 amplitude compared to adolescents without relevant psychopathology. To assess this possibility, the discordant pairs were compared to both the concordant pairs and the diagnosis-free twin pairs with a repeated measures ANOVA with an arbitrary designation of twin status as a single within-pairs factor with two levels (Twin 1, Twin 2) and two between-subjects factors: (a) sex with two levels (male, female), and (b) group with three levels (discordant, concordant, diagnosis-free). Descriptive statistics for P300 amplitude, P300 latency, reaction time and task error rate for each group are provided in Table 1, and ERP grand averages are presented in Fig. 1. The designation of a participant as Twin 1 or Twin 2 was random and therefore the repeated measures approach was used primarily to control for the presence of related individuals within groups rather than to assess a within-pairs effect of theoretical significance. As expected, there was no within-subject effect for the arbitrary twin designation on amplitude [$F(1, 327) = 0.115, P = 0.734$] and twin designation did not interact with sex [$F(1, 327) = 1.427, P = 0.233$] or with group [$F(2, 327) = 1.215, P = 0.298$]. There was no three-way interaction between twin status, sex and group [$F(2, 327) = 0.441, P = 0.643$]. Females, again, had significantly greater P300 amplitude than males [$F(1, 327) =$

Table 2
Descriptive statistics for substance use measures for members of discordant twin pairs

Variable	MZ		DZ		Total	
	Affected	Unaffected	Affected	Unaffected	Affected	Unaffected
Substance use measures—median (25th–75th percentiles)						
<i>Males</i>						
Number of drinks last year	180 (54–65)	48 (0–105)	300 (78–1040)	0 (0–36)	180 (60–780)	0 (0–72)
Years since first drink	3 (1.5–4)	2 (1–3)	3 (2–4)	2 (1–3)	3 (2–4)	2 (1–3)
Maximum number of drinks in 24 h	16 (11–24)	12 (4–15)	20 (13–29)	7 (3–22)	16 (12–24)	12 (4–17)
Number of tobacco uses in typical month	5 (0–278)	1 (0–19)	51 (2–428)	5 (0–110)	9 (0–368)	1 (0–30)
Number of street drug uses	1 (0–13)	0 (0–2)	2 (0–12)	0 (0–72)	1 (0–12)	0 (0–1)
<i>Females</i>						
Number of drinks last year	140 (77–585)	12 (0–90)	150 (0–910)	18 (0–265)	140 (57–683)	12 (0–98)
Years since first drink	2 (1–4)	1 (0–3)	3 (2–3)	2 (1–4)	2 (2–3)	1 (1–3)
Maximum number of drinks in 24 h	11 (7–20)	6 (3–8)	12 (9–24)	6 (5–9)	12 (7–21)	6 (3–8)
Number of tobacco uses in typical month	83 (0–413)	0 (0–218)	300 (6–390)	45 (0–300)	180 (2–39)	1 (0–255)
Number of street drug uses	3 (0–27)	0 (0–2)	20 (0–50)	0 (0–11)	7 (0–32)	0 (0–2)

10.400, $P = 0.001$]. Further, there was a significant effect for group membership [$F(2, 327) = 4.081$, $P = 0.018$]. The least-significant difference test was used as a post-hoc comparison of group differences in P300 amplitude. The discordant twins ($P = 0.001$) and the concordant twins ($P = 0.035$) had significantly smaller amplitudes than the diagnosis-free twin pairs, but did not differ significantly from each other ($P = 0.731$). Although the effects seem weaker in females, sex and group did not interact significantly [$F(2, 327) = 1.493$, $P = 0.226$] to influence amplitude.

Repeated-measures ANOVAs with the same design were conducted with P300 latency, reaction time, and task performance error data as well. There were no significant within-pairs or between-subjects main or interaction effects for either latency or reaction time. There was no significant within-pair effect for error rate

Table 3

Percentage of affected and unaffected twins discordant for alcoholism with diagnoses of CD, ODD, ADHD, street drug abuse/dependence (DRUG), and nicotine dependence (NIC)

	Alcohol abuse/dependence present						Alcohol abuse/dependence absent				
	N	CD	ODD	ADHD	DRUG	NIC	CD	ODD	ADHD	DRUG	NIC
<i>Male</i>											
MZ	26	65.4	26.9	11.5	19.2	34.6	46.2	26.9	19.2	15.4	19.2
DZ	16	81.3	50.0	12.5	18.8	50.0	43.8	43.8	25.0	0.0	25.0
Total	42	71.4	35.7	11.9	19.0	40.5	45.2	33.3	21.4	9.5	21.4
<i>Female</i>											
MZ	16	18.8	43.8	12.5	25.0	37.5	6.3	31.3	0.0	0.0	18.8
DZ	14	57.1	64.3	7.1	50.0	64.3	21.4	42.9	0.0	14.3	57.1
Total	30	36.7	53.3	30.0	36.7	50.0	13.3	36.7	0.0	6.7	36.7

[$F(1, 324) = 0.044, P = 0.834$], but females made significantly more errors than did males [$F(2, 324) = 14.144, P < 0.001$]. Sex and group status did not interact significantly to influence error rate [$F(2, 324) = 0.086, P = 0.918$], nor was there a main effect for group [$F(2, 324) = 0.397, P = 0.673$].

3.4. Differences in substance use between unaffected members of discordant pairs and members of concordant and diagnosis-free pairs

Because of the defining characteristics of the groups, it was expected that they would differ in substance use measures. Of interest was whether the alcohol disorder free members of discordant pairs would differ from either the members of the concordant pairs or the diagnosis-free pairs in terms of these variables. The substance use measures of unaffected members of discordant pairs were compared with the Wilcoxon Rank Sum test to those of a group composed of randomly selected members from each concordant pair. A similar comparison of substance use was made between the alcohol disorder free members of the discordant pairs and a group of randomly selected representatives of the diagnosis-free twins. The number of participants from discordant twin pairs missing substance use data has already been provided. The following number of subjects from the concordant pairs were missing the following measures: estimated alcohol consumption (one female), maximum alcohol consumption (one male, one female), years since first drink (one female), number of street drug uses (one female), and tobacco consumption (two males, one female). The following numbers of twins were missing the data in the diagnosis-free group: estimated alcohol consumption (three females), and maximum alcohol consumption (three males, three females). Descriptive statistics for these substance use measures are provided in [Table 4](#).

The unaffected members of the discordant male pairs had consumed significantly less alcohol in the previous year [$Z = 5.017, P < 0.001$], had started drinking at a later age [$Z = 4.329, P < 0.001$], and had drunk less in a 24 h period [$Z = 3.002, P = 0.003$], than the participants from the concordant male pairs. They also had smoked less tobacco in a typical month [$Z = 3.379, P = 0.001$] and had used street drugs fewer times [$Z = 2.289, P = 0.022$] than the participants from the concordant pairs. The alcohol use disorder free members of female discordant pairs also had drunk less in the previous year [$Z = 2.660, P = 0.008$], had started drinking at a later age [$Z = 2.347, P = 0.019$], and had consumed fewer drinks in 24 h [$Z = 3.403, P = 0.001$] than the participants from the concordant female pairs. They did not differ significantly in tobacco consumption [$Z = 1.833, P = 0.067$] but had used street drugs fewer times [$Z = 2.012, P = 0.044$].

Further, the unaffected members of discordant male pairs had consumed more alcohol in the past year [$Z = 3.718, P < 0.001$], had more years since their first drink [$Z = 3.949, P < 0.001$], and had a higher maximum consumption in 24 h [$Z = 6.015, P < 0.001$] than the members from the diagnosis-free female pairs. They also had consumed more tobacco in a typical month [$Z = 4.911, P < 0.001$] and taken street drugs more times [$Z = 4.709, P < 0.001$]. Similarly, unaffected members of discordant female pairs had drunk more in the past year [$Z = 4.879, P < 0.001$], had

more years since their first drink [$Z = 4.335$, $P < 0.001$], and had a higher maximum consumption in 24 h [$Z = 5.352$, $P < 0.001$] than the members from the diagnosis-free female pairs. They, too, had consumed more tobacco in a typical month [$Z = 4.689$, $P < 0.001$] and taken street drugs more times [$Z = 4.190$, $P < 0.001$].

3.5. Twin pair P300 amplitude similarity

The lack of within-pair effects in the previous repeated measures analyses are ambiguous regarding the relative contribution of genetic and environmental variation to P300 amplitude in the discordant twins. The lack of a significant effect for an alcohol use disorder in such analyses does not require that members of discordant twin pairs resemble each other, or if they do, inform us as to the relative contribution of genetic and environmental variation to this familial resemblance. Of particular interest is the possibility that members of discordant pairs may produce P300 amplitude that is under substantially less genetic influence than in the diagnosis-free pairs because of environmental influences associated with substance use. Twin pair similarity was determined using the intraclass correlation. An initial examination of the intraclass correlations suggested that they did not differ by sex, so in order to facilitate exposition, the data were sex-corrected by taking the residuals produced from the regression equation predicting P300 amplitude in the entire MTFS 17-year-old sample by a dichotomous dummy variable coded for sex. These sex-corrected data were used in calculating the intraclass correlations presented in Table 5. Since it was anticipated on theoretical grounds that members of twin pairs would resemble one another, a one-tailed test of significance was used to determine if correlations were significantly different from zero. Similarly, because it was anticipated that MZ twins would be more similar than DZ twins, one-tailed tests were used to determine if MZ similarity was greater than DZ twin similarity. Comparisons of MZ twin pairs across groups were made with two-tail tests, as were comparisons of DZ pairs.

In all three groups the MZ pairs were significantly similar, but of the DZ twins only those in the diagnosis-free pairs were significantly correlated. The MZ twin similarity was not significantly different across the three groups. Discordant MZ pair similarity was not significantly different from concordant MZ pair similarity [$Z = 0.23$, $P = 0.82$] or diagnosis-free MZ pair similarity [$Z = 1.17$, $P = 0.24$]. Similarly, discordant DZ pair similarity was not significantly different from that of concordant [$Z = 0.18$, $P = 0.86$] or diagnosis-free [$Z = 1.13$, $P = 0.26$] DZ pair similarity. Discordant MZ pairs were significantly more similar to each other than the discordant DZ pairs [$Z = 2.23$, $P = 0.01$]. The same was also true in the diagnosis-free group [$Z = 3.40$, $P < 0.001$]. Although the difference in similarity between concordant MZ and DZ pairs was in the expected direction, it was not significant statistically [$Z = 1.35$, $P = 0.09$].

Table 4

Descriptive statistics for the substance use measures for concordant and diagnosis-free twins

Variable	Concordant pairs			Diagnosis-free pairs		
	<i>N</i>	Median	(25th–75th Percentile)	<i>N</i>	Median	(25th–75th Percentile)
<i>Male Twin 1</i>						
Number of drinks last year	20	35	(180–1291)	74	0	(0–0)
Years since first drink	20	350	(3–5)	74	0	(0–2)
Maximum number of drinks in 24 h	19	16	(13–24)	73	1	(0–5)
Number of tobacco uses in typical month	18	120	(5–338)	74	0	(0–0)
Number of street drug uses	20	2	(0–6)	74	0	(0–0)
<i>Male Twin 2</i>						
Number of drinks last year	20	210	(72–982)	74	0	(0–0)
Years since first drink	20	3	(2–5)	74	0	(0–1)
Maximum number of drinks in 24 h	20	17	(12–24)	72	1	(0–3)
Number of tobacco uses in typical month	18	65	(4–300)	74	0	(0–0)
Number of street drug uses	20	0	(0–5)	74	0	(0–0)
<i>Female Twin 1</i>						
Number of drinks last year	18	150	(44–683)	146	0	(0–0)
Years since first drink	18	3	(2–4)	148	0	(0–1)
Maximum number of drinks in 24 h	18	13	(7–21)	146	1	(0–4)
Number of tobacco uses in typical month	18	62	(4–300)	148	0	(0–0)
Number of street drug uses	18	2	(0–23)	148	0	(0–0)
<i>Female Twin 2</i>						
Number of drinks last year	19	180	(90–780)	147	0	(0–0)
Years since first drink	19	3	(2–3)	148	0	(0–2)
Maximum number of drinks in 24 h	19	14	(10–18)	147	1	(0–3)
Number of tobacco uses in typical month	19	50	(1–300)	148	0	(0–0)
Number of street drug uses	19	16	(0–96)	148	0	(0–0)

Note: One member of each twin pair was randomly assigned to Twin 1 or Twin 2 status, the co-twin receiving the converse assignment. Twin 1 was used as comparison subject in analyses contrasting the unaffected members of discordant pairs to members of concordant and diagnosis-free pairs.

4. Discussion

In the present study, there was no systematic effect of having an alcohol use disorder on P300 amplitude in members of adolescent twin pairs discordant for alcohol abuse/dependence. This was true despite discordant twins having significantly less alcohol, street drug, and tobacco use. P300 amplitude in these discordant pairs was comparable to that in pairs concordant for alcohol abuse/dependence and was significantly reduced relative to pairs of low risk twins free of alcohol use disorders and related psychopathology. These differences were not present for P300 latency, reaction time, or error rate suggesting that amplitude differences were not due to differences in stimulus processing time or task engagement. Although girls had larger amplitudes than boys did, sex did not interact with twin pair status to influence P300 amplitude, suggesting that P300 indexes risk status in adolescent girls as well as boys.

Further, members of both male and female discordant MZ pairs evidenced significant within-pair similarity, suggesting a familial influence on P300 amplitude in this high-risk group. This familial resemblance among discordant pairs was not significantly different from that in concordant and diagnosis-free pairs. The DZ discordant twin pairs did not evidence correlation significantly different from zero. Members of MZ pairs were more similar than were DZ cotwins, suggesting a genetic source for the familial influence (at least in the discordant and diagnosis-free pairs). Larger samples would be needed to fit the biometrical models necessary to test for differences between discordant, concordant, and diagnosis-free groups in the genotypic architecture of P300 amplitude.

4.1. Substance use measures

The absence of P300 amplitude differences between those with and without an alcohol use disorder in the discordant twin pairs was not due to comparable substance use histories. For the most part the alcoholic twins consumed more alcohol, tobacco, and street drugs than did their cotwins. In the few cases where the affected and unaffected members of the discordant pairs did not differ on a substance use measure there was no systematic relationship between that measure

Table 5

Intraclass correlations for P300 amplitude in alcohol abuse/dependence discordant, concordant and diagnosis-free twin pairs

	N_{MZ}	r_{MZ}	N_{DZ}	r_{DZ}
Discordant pairs	42	0.55***	30	0.06
Concordant pairs	28	0.59***	11	0.13
Diagnosis-free pairs	156	0.68***	66	0.31**

Correlations are based on sex-corrected data. *P*-values are one-tailed.

** *P* < 0.01.

*** *P* < 0.001.

and P300 amplitude. It seems unlikely that the unaffected members of the discordant pairs had comparable P300 amplitude to their cotwins because of comparable substance use. The unaffected members of the discordant pairs had also used substances less than members of concordant pairs, but had consumed more than members of the diagnosis-free pairs, possibly reflecting their intermediate risk status for substance involvement. These findings leave open the possibility that the unaffected discordant cotwins have nevertheless reduced their P300 amplitude via the toxic effects on their brains from the chemicals they used. It should be emphasized, however, that (a) the unaffected twins had reduced substance use, (b) substance use was not correlated with P300, and (c) regardless how much substance was used the affected twin has a clinical disorder absent in the other twin.

4.2. *Comorbid externalizing psychopathology*

The members of the discordant pairs with an alcohol use disorder diagnosis also had a high rate of comorbid CD. The rates of CD were higher in the affected members of the male discordant twin pairs, but were comparable between affected and unaffected members of the female pairs. CD is a common disorder in the offspring of alcoholics (see [Monteiro and Schuckit, 1988](#); [Pihl et al., 1990](#); [Sher et al., 1991](#); [West and Prinz, 1987](#)), and it has been suggested that the P300 amplitude deficit in those at high-risk for alcoholism may be due to a relationship between CD and P300 amplitude. In two recent studies using different tasks, [Bauer and Hesselbrock \(1999a,b\)](#) found that P300 amplitude was reduced in adolescent males and females with more than the median number of CD symptoms for their gender, but did not differ based on a family history of alcoholism or other types of substance dependence. Further [Bauer \(1997\)](#) examined P300 amplitude in abstinent cocaine abusers and found that a subcomponent, P3a, was significantly and inversely correlated with the number of retrospectively assessed childhood CD symptoms. The correlation between childhood CD and P3a amplitude was still significant after partialing out variance due to the number of years of alcohol and cocaine use. [Carlson et al. \(1999\)](#) found that a significantly greater proportion (61.3%) of adolescent males with the smallest amplitudes from the MTFS sample had an externalizing disorder diagnosis than did those with the largest amplitudes (29%). The most prevalent externalizing disorder in each group was CD. The relationship between P300 amplitude and CD is also consistent with findings from studies suggesting a P300 amplitude reduction in adults with Antisocial Personality Disorder—a disorder that requires a premorbid diagnosis of CD before age 15 ([Bauer et al., 1994a,b](#); [Costa et al., 2000](#); [O'Connor et al., 1994a](#)).

On the other hand, CD may be only one indicator of a behavior disorder phenotype reflected by reduced P300. The affected and unaffected members of the discordant twin pairs had comparable rates of ODD, ADHD, and nicotine dependence. [Iacono et al. \(1999\)](#) reported reduced P300 amplitude with increasing numbers of disinhibited behavior indicators only one of which was a diagnosis of CD. Further, although [Iacono et al. \(2002\)](#) found reduced P300 in adolescent males from the MTFS who had a diagnosis of CD but no diagnoses of substance use

disorders or other externalizing disorders, the same was true for adolescents with comorbidity free diagnoses of (a) ODD, (b) alcohol abuse/dependence, and (c) nicotine dependence. There is accumulating evidence that several disorders involving disinhibited behavior may share common genetic risk factors. Twin studies suggest that a common set of genetic influences contribute to both adolescent use of (Koopmans et al., 1997) and adult dependence on (True et al., 1999) nicotine and alcohol. Further, there is some evidence from twin studies of a common genetic influence on CD (McGue et al., 1992; Slutske et al., 1998) or antisocial personality disorder (Grove et al., 1990; Pickens et al., 1995) and alcoholism. Perhaps reduced P300 amplitude is a marker for the broader externalizing phenotype suggested by factor analysis of epidemiological data (Kendler et al., 1997; Krueger, 1999; Krueger et al., 2001) and biometrical modeling of twin covariance patterns across disorders (Krueger et al., 2002; Young et al., 2000) rather than for alcoholism or substance abuse more narrowly construed.

4.3. Specificity of P300 amplitude as a marker of risk

P300 amplitude may be a marker of genetic risk for a broad externalizing phenotype including alcoholism, but it might not be specific to this class of psychopathology. Reduced P300 has been reported in subjects with other types of psychopathology, notably schizophrenia and major depression (e.g. Diner et al., 1985; McCarley et al., 1991; Wagner et al., 1997). P300 may be either a state or trait marker for these disorders, and there is some evidence suggesting that P300 is related to familial risk for at least some of these conditions (e.g. Blackwood et al., 1991; Frangou et al., 1997; Kidogami et al., 1991). In fact, reduced auditory P300 amplitude has been reported in both members of MZ twin pairs discordant for schizophrenia (Weisbrod et al., 1999). A P300 amplitude marker for schizophrenia risk is not, however, supported by examination of children in high-risk samples (Friedman and Squires-Wheeler, 1994). Further, calling into question the specificity of reduced P300 to externalizing phenotypes, van der Stelt (1999) found that reduced P300 was related to both higher levels of externalizing and internalizing (i.e. anxiety and depression) problems in the children of alcoholics. It is unclear if the internalizing problems preceded or were a consequence of the externalizing problems. P300 amplitude is influenced by a number of phenomena, and it may be that different sets of genes influencing different processes indexed by P300 are differentially sensitive to different types of psychopathology. For example, Johnson (1986) proposed a model of P300 amplitude involving three dimensions: the expectancies regarding the probability of the eliciting stimulus, the meaning of the stimulus to the subject, and the extent to which information regarding the stimulus is transmitted to systems involved in its cognitive processing. It is possible that comparable reductions in P300 amplitude could be seen in people at risk for unrelated forms of psychopathology because of deficits in different cognitive processes related to these dimensions. Attempts to isolate the processes leading to reduced P300 amplitude in different types of psychopathology and assessment of the specificity of these deficits to a given class of psychopathology would greatly help the

establishment of P300 as a marker. Further, prospective studies comparing P300 amplitude and psychiatric outcome in children differing in familial risk for a variety of disorders will help us estimate the specificity and sensitivity of P300 amplitude as a marker of alcoholism or externalizing psychopathology.

5. Conclusions

This study was the first to employ the discordant twin method to study P300 amplitude in members of alcohol abuse/dependence discordant twin pairs. Although one must always take caution in accepting null findings, the results suggest that in adolescence reduced P300 amplitude indexes risk for an alcohol used disorder rather than the expression of alcoholism. This finding is consistent with findings from other types of high-risk groups (e.g. non-alcoholic children of alcoholics). Further, genetic influences on P300 are implicated in the discordant twins, which is consistent with visual P300 amplitude serving as a biological trait marker of alcoholism vulnerability.

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