

P3 Event-Related Potential Amplitude and the Risk for Disinhibitory Disorders in Adolescent Boys

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Background: The children of parents who abuse alcohol typically show reduced amplitude of the P3 event-related potential wave. We determined if this effect was present in a population-based sample of older adolescent boys, whether it was associated with paternal antisocial personality and drug use, and whether it appeared in youth with childhood externalizing and substance use disorders.

Methods: A statewide sample of 502 male youth, identified from Minnesota birth records as members of twin pairs, had their P3 amplitude measured, using a visual oddball paradigm when they were approximately 17 years old. Structured clinical interviews covering attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, antisocial personality disorder, and substance use disorders were administered in person to the youth and his parents at the time of the P3 assessment and again to the youth 3 years later.

Results: Reduced P3 was associated with disorders and paternal risk for disorders, reflecting a behavioral disinhibition spectrum that included attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, antisocial personality disorder, alcoholism, nicotine dependence, and illicit drug abuse and dependence. Reduced P3 at age 17 predicted the development of substance use disorders at age 20. Most effect sizes associated with these group differences exceeded 0.70, indicating medium to moderately large group differences. Maternal alcoholism and substance use during pregnancy were unrelated to P3 amplitude in offspring.

Conclusion: Small amplitude P3 may indicate genetic risk for a dimension of disinhibiting psychiatric disorders, including childhood externalizing, adult antisocial personality disorder, and substance use disorders.

Arch Gen Psychiatry. 2002;59:750-757

R ESEARCH INDICATES that, compared with the sons of men without alcoholism, the sons of parents who abuse alcohol show reduced amplitude of the P3 component of the electrocortical event-related potential,¹ supporting the hypothesis of Begleiter et al² that P3 amplitude has potential as a biological marker for alcoholism risk. Nevertheless, many relevant issues have not been systematically addressed. Investigators have most often recruited subjects at risk for alcoholism by identifying parents in treatment settings and studying their children.²⁻²⁰ Such samples are likely to represent particularly severe cases of alcoholism, an ideal place to begin a search for biological markers, but replication in community samples is needed. Other studies have recruited high-risk subjects by means of advertisements soliciting volunteer offspring of parents who abuse alcohol²¹⁻²⁵ or by screening under-

graduate volunteers for a family history of alcoholism.²⁶⁻²⁸ Although each source has its advantages, participants who volunteer in response to advertisements and undergraduate recruits may be unusual in several important respects and are not representative of the population of individuals with paternal histories of alcoholism. To our knowledge, there have not yet been any studies assessing P3 amplitude in the sons of parents who abuse alcohol ascertained from an unselected community-based sample representative of subjects with alcoholism in the general population.

Reduced P3 amplitude is not unique to alcoholics and their children but has been reported for several related phenotypes. Several important childhood psychiatric disorders, such as attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder, have been associated with risk for alcoholism.²⁹⁻³³ These externalizing disorders have also

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SUBJECTS AND METHODS

SUBJECTS

Participants, aged 16.6 to 18.3 years (mean \pm SD, 17.5 \pm 0.4 years), consisted of 502 male youth (226 twin pairs and 50 unmatched twins) from the older cohort of the Minnesota Twin Family Study. All were identified from birth records as twins born in Minnesota between January 1, 1972, and December 31, 1978 (a thorough description of the Minnesota Twin Family Study research design, sample characteristics, and diagnostic procedures can be found elsewhere⁵¹). Three years later, 417 youth (83%) (mean \pm SD age, 20.7 \pm 0.5 years) returned for a follow-up assessment. Consistent with the demographics of the state of Minnesota at the time the boys were born, most (99%) were white. Participants' biological fathers ranged in age from 32.2 to 66.1 years (mean \pm SD, 46.7 \pm 5.5 years), and mothers from 33.0 to 59.4 years (mean \pm SD, 44.4 \pm 4.5 years). All youth and their parents gave written informed assent or consent as appropriate.

Adolescents were split into psychiatric risk groups depending on their study intake diagnoses and whether they developed (for the first time) a substance use disorder between the ages of 17 and 20. To achieve consistency with existing research on P3 in the sons of parents who abuse alcohol, participants were also divided into paternal risk groups based on their father's family history, history of alcohol consumption, and diagnosis. A nonpsychiatric comparison group was composed of participants free of psychiatric disorders whose fathers did not have a serious drinking history; antisocial, alcohol, or illicit drug use disorders; or first-degree male relatives with a history of alcohol-related problems. Those nonpsychiatric subjects who returned for their follow-up assessment and were still free of substance use disorders served as the comparison group for the analysis of the longitudinal data.

ASSESSMENTS

Trained master's and bachelor's level interviewers conducted structured in-person interviews of mothers, fathers, and their sons independently in our university laboratory. Adolescents were interviewed with a revised version of the Diagnostic Interview for Children and Adolescents⁵² and a modified version of the Composite International Diagnostic Interview⁵³ expanded Substance Abuse Module.⁵⁴ Mothers were interviewed about their sons, using the parent version of the Diagnostic Interview for Children and Adolescents, enabling the assignment of *DSM-III-R*⁵⁵ diagnoses of the youth by combining mother and son interview data, using a "best-estimate" approach.⁵⁶ At the follow-up assessment, the 20-year-old men received the Substance Abuse Module and served as sole informants about themselves.

Fathers and mothers were interviewed about themselves, using the Substance Abuse Module, and both were interviewed about the father's first-degree male relatives, using a composite interview derived from the Family History-Research Diagnostic Criteria⁵⁷ and Family Informant Schedule and Criteria.⁵⁸ In addition, fathers were given

an ASPD interview specially developed for the Minnesota Twin Family Study.⁵⁹

Except for a diagnosis of substance abuse, which is based on the presence of a single symptom, adolescents and their parents were considered to have a lifetime study diagnosis if all *DSM-III-R* symptom criteria were satisfied (definite certainty level) or all criteria but 1 were satisfied (probable certainty level). Cohen κ reliability coefficients for the various disorders of interest in the present study ranged from 0.71 (oppositional defiant disorder) to more than 0.90 (for ASPD and substance diagnoses).⁵¹

Because we were working with a population-based rather than a treatment sample, we were concerned about potential false-negative diagnoses stemming from our participants' possible desire to downplay their drinking problems. Because quantitative traits can enhance the study of qualitative phenotypes, serving as a "useful proxy for alcoholism diagnoses,"^{60(p636)} we examined 2 quantitative measures that are associated with vulnerability to alcoholism: age at first use of alcohol⁶¹⁻⁶⁴ and maximum number of drinks consumed in a 24-hour period.^{60,65} We combined these 2 measures such that fathers in the most deviant decile of the distribution on either alcoholism-related phenotype were considered to have a significant drinking history. This identified 35 "affected" fathers (with 65 sons in the sample) whose drinking history was considered significant in the absence of a diagnosis of dependence. If either the father or the mother reported that any first-degree male relative of the father's had at least 2 drinking problems (from a list including physical fights, loss of friends, and legal, financial, medical, family, school, or work difficulties) or had ever been treated for alcoholism, paternal family history was coded as positive. Ninety-one subjects had a positive history of alcoholism in the father's immediate family by this measure in the absence of alcohol dependence in the 48 fathers themselves. These 48 fathers served as the "affected" group.

PROCEDURES

We used the rotated-heads oddball paradigm² illustrated in **Figure 1**. In this task, subjects watched 240 computerized stimuli consisting of an oval (two thirds of the trials) or a stylized head (one third of trials) and indicated by button press on which side of the head its ear appeared. Stimulus duration was 98 milliseconds, with the intertrial interval varying randomly between 1 and 2 seconds. Subjects were required to maintain their gaze on a fixation point that appeared in the center of the screen between trials. Subjects performed several practice trials to ensure they understood the task.

All subjects completed the procedure at the same time of late morning. Participants sat in a padded high-backed chair, and the Grass Model 12A Neurodata Acquisition System (West Warwick, RI) was used to record electroencephalographic and electro-oculographic data filtered at 0.01 to 30 Hz (half-amplitude). Electroencephalographic data were recorded from 3 parietal locations, 1 on the midline scalp (Pz) and 1 over each hemisphere (P3 and P4). Linked

Continued on next page

been associated with reduced P3 amplitude.³⁴⁻³⁹ Moreover, adult subjects with a substance use disorder defined more broadly^{40,41} or with antisocial personality dis-

order (ASPD)^{24,42-44} tend to have reduced P3 amplitudes. Consistent with these findings, reduced P3 amplitude appears to be associated with risk for substance abuse in

earlobes served as reference and an electrode on the right shin as ground. Blinks and eye movements were recorded with a pair of biopotential electrodes arranged in a transverse montage, one electrode superior to the eye and the other over the outer canthus. Impedances were below 5 k Ω for scalp electrodes and below 10 k Ω for electro-oculographic recordings. For each trial, 2 seconds of electroencephalographic or electro-oculographic data, including a 500-millisecond prestimulus baseline, were digitized to 12-bits resolution at a rate of 256 Hz. Target trials were repeated if the subject failed to respond or if the limits of the analog-to-digital converter were exceeded.

Blinks and other ocular artifacts in the electroencephalographic data were corrected offline by a computer algorithm.⁶⁶ We digitally filtered the mean event-related potentials, using a frequency-sampled finite impulse response low-pass filter with least squares error and a transition band.⁶⁷ The cutoff frequency of this zero-phase filter (attenuation of 3 dB) was approximately 7.56 Hz, and it resulted in 40-dB attenuation of the signal at 11.56 Hz.

Using a computer algorithm, we determined the point of maximum amplitude in each waveform between 250 and 800 milliseconds. One of several trained individuals, guided by the characteristics of waveforms recorded at other electrode locations, monitored the algorithm to ensure that the point chosen was in fact the P3 wave, defined as the most prominent positive peak in this time interval. If the waveform in this interval consisted of 2 closely spaced peaks of approximately equal amplitude, suggesting separate P3a and P3b peaks,⁶⁸ we selected the second, which would correspond to P3b.

STATISTICAL ANALYSIS

Analyses consisted of 2-tailed *t* tests and analyses of variance, with significance established at *P* = .05. Effect sizes (Cohen *d*) were computed, using the SD of the entire sample (7.79 μ V). We assessed associations between P3 amplitude and measures of alcohol consumption and illicit drug use with Kendall τ rank correlation coefficient, owing to the nonnormal distribution of many of these measures and because it is superior to Spearman rank correlation coefficient in cases of tied ranks. In the analysis of paternal risk, hierarchical linear modeling was used to examine group differences, and a random regression model was used to calculate odds ratios (ORs) to account for the correlated nature of the twin data. Such analyses were not applied to the evaluation of adolescent psychiatric disorders, in which twin pairs were often split across diagnostic groups. Instead, we reduced the *df* for each analysis (by using as the *df* the number of twin pairs rather than the number of participants) and recalculated the appropriate *P* value. Because in no case did a significant finding become nonsignificant, we report herein the unadjusted *df* and *P* values.

To determine if adolescents with childhood externalizing psychiatric disorders and substance use disorders had reduced P3, we divided participants into diagnostic groups and contrasted their P3 amplitude with that of the comparison subjects. Two different approaches to grouping participants were taken. One involved assigning subjects to different diagnostic categories without consideration of any

possible comorbid diagnoses. These “comorbid group” analyses included all participants, and the resulting diagnostic groupings contain a representative sample of individuals with the diagnosis. The other grouping strategy involved forming nonoverlapping diagnostic groups of individuals who had none of the other diagnoses. This “pure group” approach made it possible to evaluate the effect of having just the designated disorder, because participants with multiple diagnoses were omitted from the analysis.

To determine if paternal risk was associated with P3 amplitude in offspring, we separated adolescents into overlapping groups based on 5 paternal characteristics. We identified as “affected” those fathers diagnosed as having (a) alcoholism or a sibling or parent with alcoholism, (b) drug abuse or dependence, or (c) ASPD. Also considered as affected were those fathers (d) with a sibling or parent with alcoholism or (e) who fell into the most deviant decile of drinking behavior. These analyses were carried out twice, first considering all the offspring of fathers with the diagnoses of interest, and then considering only those offspring who had not themselves developed a substance use disorder.

Although the comparison group of 71 participants was free of individuals with an externalizing disorder or affected father, 19 of these participants subsequently developed a substance use disorder at age 20 (another 8 had not completed their follow-up assessment at the time of this report). These 19 new abusers had significantly smaller P3 amplitude (by 7.12 μ V) at age 17 (mean \pm SD, 22.76 \pm 9.03 μ V) than the remainder of this group (mean \pm SD, 29.87 \pm 9.20 μ V) (t_{61} = 2.81, *P* = .007). Using this still unaffected group of 44 as the control group, all adolescents developing a substance use disorder between the ages of 17 and 20 who did not already have such a diagnosis at age 17 were examined to determine if they had smaller P3 amplitudes at age 17 than the controls.

To simplify the presentation of the data, several preliminary analyses were carried out. Although 3 recording sites were used, P3 amplitude at the 3 sites was highly correlated (r = 0.87 for Pz-P3 and Pz-P4). In addition, recent evidence indicates that children of parents who abuse alcohol differ from children of parents who do not abuse alcohol with respect to P3 amplitude but not its scalp distribution.¹⁷ Given these findings, to ease understanding of the results and to facilitate comparison with the many studies that have reported primarily Pz data, we analyzed data from Pz only. Because P3 amplitude for the easy and hard conditions (Figure 1) was also highly correlated (r = 0.87), we calculated P3 amplitude from the mean of the easy and hard trials combined. None of the high-risk groups differed significantly from the comparison participants in P3 latency or in manual reaction time for correct responses (all t < 1.78). Finally, with 1 exception, performance accuracy (percentage of hits out of 80 target trials) failed to significantly differentiate comparison participants from any other group. The 1 exception involved the comorbid attention-deficit/hyperactivity disorder group, which averaged 1 fewer hit (mean, 78.09 hits) than the comparison group (mean, 79.10 hits) (t_{112} = 3.34, *P* < .01). Given these findings of no significant effect for latency and reaction time and little effect for hit rate, these variables were not considered further.

general, not just alcoholism,^{45,46} and reduced P3 in pre-adolescence may predict subsequent substance use and alcoholism in adolescence.^{6,23}

The results of these and other studies have led to proposals that P3 amplitude is a candidate endophenotype associated with vulnerability to a broad spectrum

of disinhibited psychiatric disorders, including externalizing psychiatric syndromes and substance abuse.^{47,48} This makes it imperative to assess relevant psychiatric disorders in studies using P3 amplitude as a risk indicator, a strategy that has been applied only selectively in this extensive literature.*

A third unresolved issue concerns the role of maternal substance use during pregnancy in relation to P3 amplitude. Studies of P3 amplitude and alcoholism risk have typically excluded subjects whose mothers had a diagnosed substance use disorder (for an exception, see Hill et al⁸). This strategy, while controlling for effects of maternal alcoholism, does not necessarily control for any effects of alcohol consumption during pregnancy. Moreover, given the tendency toward assortative mating, ie, for spouses to select each other on the basis of shared characteristics, such a strategy is also likely to bias the samples used. It would thus seem desirable to systematically assess any effects on P3 amplitude of maternal substance use disorders and substance use during pregnancy.

In the present investigation, we hypothesized that P3 amplitude findings observed previously in convenience samples would be evident in a general population sample. Specifically, we predicted that P3 amplitude reduction in adolescent youth would be associated with a range of substance and externalizing disorders and with a history of paternal substance abuse. In addition, we expected P3 amplitude at age 17 to predict the development of substance use disorders at age 20.

RESULTS

ADOLESCENT P3 AMPLITUDE AND PSYCHIATRIC DISORDERS

The results of the P3 analyses are summarized in **Table 1** and **Figure 2**. All but 3 of the comparisons between the diagnostic groups and controls were statistically significant. The 3 nonsignificant comparisons involved pure groups, and 2 involved groups with fewer than 10 subjects. All of the significant analyses were associated with an effect size of 0.49 or larger (median, 0.73). Those with externalizing or substance abuse psychiatric disorders differed little in their P3 amplitude, but collectively their amplitudes were about 6 μ V smaller than those of the comparison subjects.

To determine whether having a childhood externalizing and a substance use disorder was associated with having especially small amplitude P3, those with just one of these types of disorder ($n=167$) were compared with those with both ($n=89$). The P3 amplitude of those with both types was 1.9 μ V smaller (mean \pm SD, 21.51 \pm 6.55 μ V) than that of those with just 1 (mean \pm SD, 23.40 \pm 7.31 μ V), a significant effect ($t_{254}=2.03$, $P=.04$).

ADOLESCENT P3 AMPLITUDE AND PATERNAL HISTORY

We assessed the degree of similarity between paternal alcohol dependence and significant drinking history by

*References 3,11,13,17,38,39,43,45,49,50.

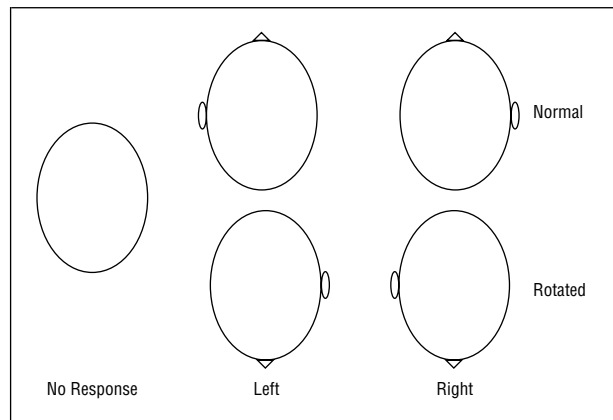


Figure 1. Schematic representation of the stimuli used in the rotated-heads task. The oval on the left was presented on 180 trials and required no response. Each pair of ovals on the right (normal and rotated) were presented on 40 occasions, and the subject was required to push a button near his left or right hand to indicate if the ear was on the right or the left side of the head. For normal heads, the side of the screen displaying the ear and the side of the head with the ear were the same (easy condition). For the rotated heads, the side of the screen displaying the ear and the side of the head with the ear were opposite (hard condition).

means of a tetrachoric correlation, assuming a normal liability distribution underlying each. The resulting correlation was highly significant (tetrachoric $r=0.57$, $P<.001$). In addition, we calculated ORs to determine whether adolescents whose fathers had a significant drinking history were significantly more likely to have an externalizing disorder than those whose fathers did not have a psychiatric diagnosis. This was indeed the case for conduct disorder (OR, 1.93; 95% confidence interval [CI], 1.23-3.05), nicotine dependence (OR, 2.31; 95% CI, 1.22-4.38), alcohol abuse or dependence (OR, 2.39; 95% CI, 1.39-4.11), and illicit drug abuse or dependence (OR, 3.01; 95% CI, 1.23-7.36).

Moreover, P3 amplitude was reduced among youths whose fathers had a significant drinking history ($n=182$; mean \pm SD, 22.26 \pm 6.81) relative to those whose fathers did not ($n=271$; mean \pm SD, 24.82 \pm 8.34) ($t_{451}=3.45$, $P=.001$). Even when subjects whose fathers had a substance use disorder or ASPD were excluded, those whose fathers had a significant drinking history had reduced P3 amplitudes ($n=61$; mean \pm SD, 21.40 \pm 6.57) relative to subjects whose fathers did not ($n=189$; mean \pm SD, 25.37 \pm 8.39) ($t_{239}=3.47$, $P=.001$), yielding an effect size of 0.54.

As **Table 2** (and Figure 2A) indicates, in all but 1 instance, father's diagnosis was associated with reduced P3 amplitude in offspring, significantly so for half of the group comparisons. The effect sizes range from 0.39 to 1.00 (median, 0.59), indicating that those with affected fathers tended to have P3s that were about 4.6 μ V smaller than those of comparison participants.

P3 AMPLITUDE AT AGE 17 AND SUBSTANCE ABUSE AT AGE 20

Figure 2B illustrates the degree to which new substance abusers had smaller P3 amplitudes than controls, and **Table 3** provides P3 values and corresponding statistics for subjects who were without a substance use disorder at age 17 but developed one by age 20. The middle

Table 1. Adolescent P3 Amplitude as a Function of Externalizing the Substance Use Diagnoses*

Adolescent's Diagnosis	Comorbid Groups						Pure Groups					
	No.	Mean (SD) P3 Amplitude, μV	df	t	P Value	Effect Size	No.	Mean (SD) P3 Amplitude, μV	df	t	P Value	Effect Size
Attention-deficit/hyperactivity disorder	45	23.50 (6.21)	114	2.51	.01	0.53	8	25.21 (4.70)	77	.69	.50	0.31
Conduct disorder	185	22.67 (7.36)	254	4.38	<.001	0.64	67	23.84 (8.24)	136	2.45	.02	0.49
Oppositional defiant disorder	87	21.97 (7.13)	156	4.18	<.001	0.73	16	21.50 (7.14)	85	2.35	.02	0.79
Nicotine dependence	69	21.75 (5.92)	138	4.26	<.001	0.76	7	20.22 (6.83)	76	1.94	.06	0.95
Alcohol abuse or dependence	95	21.61 (6.58)	164	4.72	<.001	0.78	23	23.40 (6.02)	92	1.94	.06	0.55
Illicit drug abuse or dependence	36	21.96 (6.91)	105	3.09	.003	0.73	1	18.72	NA	NA	NA	1.15

*NA indicates not applicable. Comorbid and pure groups were both compared with the 71 individuals in the nonpsychiatric comparison group (mean [SD] P3 amplitude, 27.65 [9.89]). No significant *P* value became nonsignificant when the degrees of freedom was reduced to equal the number of twin pairs rather than the number of individuals assessed.

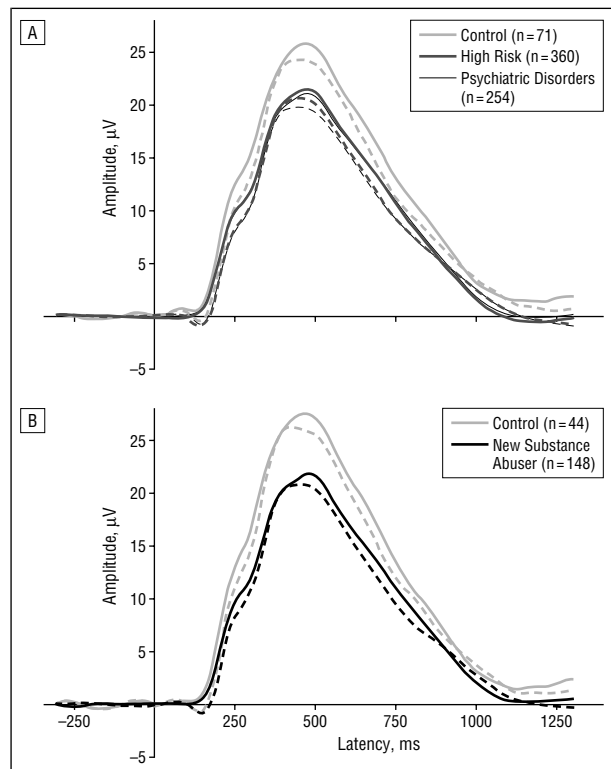


Figure 2. Grand mean event-related potentials as a function of substance abuse status: waveforms for easy (solid lines) and hard (dashed lines) trials. A, "High Risk" refers to all participants with an affected father. "Psychiatric Disorders" refers to the combined group of adolescents with a diagnosis of attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, nicotine dependence, alcohol abuse or dependence, or illicit drug abuse or dependence. "Control" refers to participants with neither an affected father nor a psychiatric disorder. B, "New Substance Abusers" refers to all participants developing a substance abuse diagnosis between their initial visit at age 17 and their follow-up visit at age 20 in the absence of any such diagnosis initially. Some of the 17-year-old control subjects developed a substance diagnosis by age 20; these individuals were not included in the control group grand means in B.

columns of the table examine the same effects when individuals with externalizing psychiatric disorders at age 17 were removed from the analysis, and the far right columns examine these effects when adolescents with an affected father were removed from the analysis. In every comparison but 1, the adolescents who developed substance use disorders had significantly smaller P3 at age 17 than the comparison group. The single exception con-

cerned individuals with unaffected fathers at age 17 who developed illicit drug disorders. Turning to individuals who had a substance use diagnosis at age 17, these participants had smaller P3s (by 1.43 μV) than those who became affected between ages 17 and 20. To formally evaluate this difference, the P3 amplitude of the 148 new substance abusers (mean \pm SD, 23.33 \pm 7.30 μV) was compared with that of the 126 previous abusers (mean \pm SD, 21.90 \pm 6.45 μV), revealing a nonsignificant effect ($t_{272} = 1.70$, $P = .09$).

IN UTERO AND MATERNAL EFFECTS

To determine whether maternal use of substances during pregnancy could account for the P3 effects, P3 amplitude was examined as a function of maternal substance use during and outside of the mother's pregnancy. The variables evaluated were any alcohol consumption, regular use of alcohol, average amount drunk per week, maximum amount drunk in a 24-hour period, any smoking, amount smoked per day, any use of illicit drugs, and lifetime history of alcohol dependence, nicotine dependence, and illicit drug abuse or dependence. All hierarchical linear modeling analyses generated nonsignificant findings (all $F < 1.50$) and, furthermore, did not suggest that maternal status on these variables might be associated with reduced P3 amplitude among the adolescent sons.

SUBSTANCE USE AND P3 AMPLITUDE

Because many participants were already using substances, to evaluate whether reduced P3 amplitude could reasonably be attributed to use rather than risk status, correlations were calculated between P3 size and various substance use measures for those with a substance use disorder (ie, those included in the groups in the bottom 3 rows of Table 1), those in a familial risk group (the top 3 rows of Table 2), and those who developed a substance use disorder between the ages of 17 and 20. Measures of substance use included lifetime number of alcohol intoxications, estimated alcohol consumption in the preceding year, number of lifetime uses of street drugs, and estimated daily consumption of tobacco products. The only significant associations were between P3 amplitude and substance use in the sons of parents who abuse

Table 2. Adolescent P3 Amplitude as a Function of Paternal History of Substance Use Disorder and Antisocial Personality Disorder (ASPD)*

Father's Diagnosis	All Offspring						Offspring With Substance Abuse Diagnoses Excluded							
	No.	Mean (SD)		df	F	P Value	Effect Size	No.	Mean (SD)		df	F	P Value	Effect Size
		P3 Amplitude, μ V							P3 Amplitude, μ V					
Alcohol abuse or dependence	337	22.95 (7.57)		229	11.92	<.001	0.51	242	23.51 (8.45)		192	7.19	.008	0.43
Illicit drug abuse or dependence	50	23.57 (13.58)		73	2.40	.13	0.40	32	23.69 (16.16)		64	1.56	.22	0.39
ASPD	44	21.43 (14.20)		69	6.21	.02	0.68	29	22.66 (16.35)		63	2.75	.10	0.52
ASPD + alcohol abuse or dependence	33	21.61 (15.95)		63	4.63	.04	0.66	19	23.24 (19.40)		57	1.44	.24	0.44
ASPD + drug abuse or dependence	19	19.95 (20.02)		55	5.06	.03	0.86	11	18.88 (25.64)		51	4.15	.047	0.85
All 3 disorders	15	20.80 (22.28)		53	3.15	.08	0.76	7	20.06 (31.36)		49	2.01	.16	1.00

*All groups were compared with the 71 individuals in the nonpsychiatric comparison group (mean [SD] P3 amplitude, 27.65 [9.89]) by means of a multilevel analysis to account for correlations between twins within groups defined by paternal status. Degrees of freedom reflects the number of different families in each analysis minus 2, representing variance components estimated by the model (variance in mean P3 amplitude among families and residual, or within-family, variance).

Table 3. How Adolescent P3 Amplitude at Age 17 Predicts the Development of Substance Use Disorders Between the Ages of 17 and 20 in Adolescents With No Substance Use Disorder at Age 17*

Adolescent's Substance Diagnosis	All Adolescents Developing a Substance Use Disorder						Adolescents With Externalizing Diagnosis at Age 17 Excluded						Adolescents With Affected Father Excluded								
	No.	Mean (SD)		df	t	P Value	Effect Size	No.	Mean (SD)		df	t	P Value	Effect Size	No.	Mean (SD)		df	t	P Value	Effect Size
		P3 Amplitude, μ V							P3 Amplitude, μ V							P3 Amplitude, μ V					
Any disorder	148	23.33 (7.30)		190	4.89	.01	0.84	87	23.13 (7.32)		129	4.54	<.001	0.87	34	23.77 (8.26)		76	3.02	.003	0.78
Alcohol disorder	126	23.74 (7.23)		168	4.49	<.001	0.79	79	23.55 (7.31)		121	4.17	<.001	0.81	28	23.96 (8.89)		70	2.68	.009	0.76
Illicit drug disorder	34	24.61 (8.10)		76	2.62	.01	0.68	12	22.22 (8.56)		54	2.57	.01	0.98	10	23.50 (9.47)		52	1.95	.06	0.82
Nicotine dependence	60	22.90 (7.46)		102	4.24	<.001	0.89	24	21.79 (7.48)		66	3.67	.001	1.04	15	23.00 (8.34)		57	2.54	.01	0.88

*All groups were compared with the 44 nonpsychiatric comparison group participants who had no substance use diagnosis at either age 17 or 20 (mean [SD] P3 amplitude, 29.87 [9.27]). No significant P value became nonsignificant when the degrees of freedom was reduced to equal the number of twin pairs rather than the number of individuals assessed.

alcohol and the sons of fathers with ASPD, and only in the groups including sons who already had developed a substance use disorder. Specifically, amplitude was inversely correlated with the lifetime numbers of street drug uses and alcohol intoxications and the estimated amount of alcohol consumed during the past year in both groups. When the analyses for these groups were repeated using these measures as covariates, the group differences in P3 amplitude remained statistically significant.

COMMENT

To our knowledge, the present report is the first study of P3 amplitude in a population-based sample of adolescent boys. It supports results of prior studies¹ derived from clinic-referred and college student samples by showing that reduced P3 amplitude is associated with paternal alcoholism. Our findings also extend this literature in several important respects. First, the P3 effect in offspring was not limited to those who abuse alcohol; a father with ASPD was likely to have a son with small amplitude P3. Second, disinhibiting psychiatric disorders in the youth were associated with P3 reduction. This was evident in youth with childhood externalizing disorders and those with substance use disorders, and it was evident in those with and without comorbid psychiatric disorders. Although not working with population-based samples or necessarily controlling for possible effects of comorbid

externalizing disorders, other researchers have also found children with these types of disorders and paternity to have small amplitude P3.^{34-39,45} Third, reduced P3 recorded in late adolescence was associated with the development of all types of substance use disorders 3 years later. This was true when analyses were limited to adolescent boys free of childhood psychiatric disorders at age 17, and when limited to boys without a paternal history of alcoholism, illicit drug abuse or dependence, or ASPD. This finding thus complements other research showing that P3 predicts substance use outcomes in preadolescent and early adolescent children.^{6,15,23} For all of these various findings, effect sizes were medium to large, with 61% (22/36) of those reported in Tables 1, 2, and 3 exceeding 0.70. Effect sizes of this approximate magnitude indicate that the overlap between our comparison and at-risk sample distributions is about 50%. Taken in combination, these findings are consistent with the hypothesis that reduced P3 in male youth is associated with vulnerability to a broad spectrum of disinhibiting psychiatric disorders, including antisocial and addictive disorders.

Because the present study was carried out with high school seniors, most participants had at least some exposure to psychoactive substances. However, it is unlikely that substance use per se accounts for the outcome. Offspring with no substance use diagnosis had reduced amplitude P3 as long as their fathers had an ex-

ternalizing diagnosis, and P3 amplitude was uncorrelated with different measures of nicotine, alcohol, and illicit drug use in most groups. Substance use was correlated with P3 in 2 groups, the sons of parents who abuse alcohol and of fathers with ASPD (but only when sons with a substance use disorder were included in these groups). When the effects of substance use were controlled for in these analyses, the P3 effects remained significant. Maternal substance use during pregnancy also seems an unlikely effect on the findings. Various measures of substance intake during pregnancy were unrelated to P3 amplitude, as was a lifetime diagnosis of substance disorder in the mother.

Recent studies have suggested that alcoholism and drug abuse,⁶⁹⁻⁷² as well as alcoholism and conduct disorder or ASPD,⁷³⁻⁷⁷ share a common genetic effect. In addition, factor analyses of the National Comorbidity Survey data indicated that a single dimension representing externalizing psychiatric disorders may underlie disorders related to substance use and antisocial behavior.^{78,79} The results of the present study, which indicate that reduced P3 is associated with disorders and familial risk for disorders reflecting externalizing behavior, suggest that reduced P3 may be associated with genetic risk for disinhibited psychiatric disorders generally.

Because diminished P3 amplitude is found in persons with depression⁸⁰⁻⁸³ and schizophrenia,⁸⁴⁻⁸⁶ it cannot be considered a diagnostic marker of externalizing disorders. However, reduced P3 has not been consistently associated with familial risk for either depression or schizophrenia, it does not predict the development of these disorders, and in these disorders it has typically been found using auditory, not visual, paradigms. These findings leave open the possibility that reduction in the visual evoked P3 may be a trait marker for externalizing psychiatric disorders. Recently, reduced P3 coupled with an electrodermal measure of response inhibition⁸⁷ was found to identify youth with much higher rates of alcohol and nicotine dependence than were evident in youth with only one of these psychophysiological attributes.⁸⁸ This finding leaves open the possibility that measurement of P3 amplitude used in conjunction with other measures has the potential to identify a multivariate endophenotype more specifically associated with externalizing psychiatric disorders.

Our study has several limitations. Although population-based, our adolescents were all from twin births. We cannot rule out the possibility that their being twins limits the generalizability of our findings. Although representative of the ethnic diversity of the Minnesota population at the time they were born, they are almost exclusively white. Whether our findings would generalize to other ethnic groups requires further investigation. We examined only adolescent boys, all of whom were approximately age 17 at study intake. Findings for girls and younger youths could be different.

Submitted for publication March 28, 2001; final revision received October 5, 2001; accepted October 12, 2001.

This study was supported by grants DA 05147 and AA 09367 from the National Institutes of Health, Bethesda, Md.

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