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Identifying a multivariate endophenotype for substance use disorders using psychophysiological measures

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Abstract

This investigation examined how reduced amplitude of the P300 event-related potential (elicited from a visual oddball task) can be used together with an electrodermal response modulation measure (indexing the ability to inhibit responsivity to a temporally predictable aversive stimulus) to identify adolescents at especially high risk to develop substance dependence. One hundred and twenty-nine 17-year-old boys were divided into groups characterized as low risk (high amplitude P300 and good electrodermal modulation), high risk (reduced amplitude P300 and poor modulation), or intermediate risk (a high or good score on one measure and a low or poor score on the other). P300 amplitude and electrodermal modulation were uncorrelated. High-risk boys had 4–6 times more alcohol dependence than intermediate or low-risk boys and 2–3 times more nicotine dependence. Performance on an antisaccade eye-tracking task in which participants directed their gaze in a direction opposite to target movement was related to electrodermal modulation but not P300 amplitude. The results from all three psychophysiological measures together suggest that the neural circuits affecting P300 amplitude and electrodermal response modulation are different and that poor electrodermal response modulation may reflect an inhibitory control deficit mediated by the frontal lobes. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Modern developments in molecular genetics have intensified the search for genes associated with alcoholism. While such efforts clearly hold

promise, the power to detect genes is limited by the inability to identify all gene carriers in a family with an alcoholic proband. The likelihood that this search will pay off would be enhanced if there existed an alcoholism-related endophenotype, some measurable characteristic of a person that can be detected with a laboratory procedure and that is itself a product of the gene or genes predisposing to alcoholism risk. As noted else-

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where (Iacono, 1998), a valid endophenotype would simplify research by: (a) lessening the likely etiologic heterogeneity present when cases are identified based on the presence of the clinical phenotype; (b) reducing both false positives and false negatives in case identification; (c) making it possible to determine the mode of genetic transmission; and (d) eliminating the requirement that only certain kinds of families (e.g., those with multiply affected members), which may not be representative of families with an alcoholic proband generally, serve as the study population.

1.1. Advantage of a multivariate endophenotype for alcoholism

Psychophysiological research currently provides the best candidate endophenotypes for substance abuse, and the P300 component of the event-related potential (ERP) is probably the single best putative endophenotype for alcoholism. In a meta-analysis of the relevant literature, Polich et al. (1994) reviewed approximately 30 investigations indicating that a paternal history of alcoholism was associated with reduced P300 amplitude in the children of alcoholics. The results indicated that P300 elicited from both auditory and visual ‘oddball’ tasks was smaller than normal in male offspring of alcoholic probands. The effect size, indicating the degree to which high risk children’s P300 was smaller than that of comparison subjects, was 0.25 across all the studies examined.

Although such results are encouraging, the P300 distributions of high risk and control children nevertheless show considerable overlap. It would be advantageous to have an endophenotype that provides even greater group differentiation, making the positive predictive power (the proportion of those with the endophenotype who are truly gene carriers) substantially higher. One way to accomplish this objective is to manipulate the task used to elicit the response. For instance, the review by Polich et al. (1994) indicated that the strongest effect sizes were associated with complex visual tasks calling for decision-guided subject responses. Another approach, however, would be to use P300 together with one or more

other putative psychophysiological endophenotypes to create, in effect, a multivariate endophenotype. Although the concept of a multivariate endophenotype for psychopathology has been applied to schizophrenia research (Grove et al., 1991; Iacono and Grove, 1993), to the knowledge of the authors, it has not been examined with substance use disorders. The goal of the present investigation was to illustrate how two psychophysiological candidate endophenotypes, when considered together, have the potential to identify individuals who are at especially high risk for alcoholism and other substance use disorders.

1.2. Findings from the Minnesota Twin Family Study using psychophysiological high risk designs

Participants for the present investigation were all male youths, approximately 17 years old, who were part of the Minnesota Twin Family Study (MTFS), an epidemiological study of Minnesota twins who attained this age at the time research subjects were recruited. Participants underwent a psychophysiological assessment that included measurement of P300 using a difficult visual task and electrodermal modulation to an aversive stimulus that varied in its temporal predictability. Findings from the MTFS support the hypothesis that each task is associated with risk for developing substance use disorders. Two lines of evidence are consistent with this conclusion. First, individual differences in key variables related to performance on both tasks appear to be heritable. For P300, a preliminary analysis by Katsanis et al. (1997) indicated substantial similarity among 30 pairs of monozygotic (MZ) twins (intra-class correlations 0.73–0.79 depending on task condition and electrode site) compared to 34 pairs of dizygotic (DZ) twins (corresponding intra-class correlations 0.19–0.47). Biometrical modeling of the twin P300 data yielded heritability estimates for P300 amplitude over 0.7, indicating that more than 70% of the variance in the expression of the trait could be attributed to genes. Other studies using different tasks to elicit P300 have also found P300 amplitude to be heritable (Boomsma et al., 1997). For electrodermal modulation, the intra-class correlation for 41 pairs of MZ twins was

0.42 compared to the correlation of 0.29 for 23 pairs of DZ twins, yielding a heritability estimate of 0.26 (Falconer method, Iacono et al., 1999).

The second factor supporting the potential of these cerebral and autonomic measures to serve as endophenotypes comes from MTFs research employing a ‘psychophysiological high risk’ design (Iacono, 1998). This approach involves selecting individuals from the general population of available subjects because they are likely to either possess or not possess the endophenotype. This can be accomplished by assessing the characteristic on all subjects, but selecting for study only those who come from the extremes of the distribution. With this research design, the usual independent and dependent variables are reversed such that the psychophysiological measure constitutes the independent variable and subject symptomatology and diagnosis serve as the dependent variables.

Carlson et al. (1999) used this method to select MTFs 17-year-old boys with either very large or very small P300 amplitude. For comparison purposes, they also selected a group from the middle of the P300 distribution, those with typical or average P300 amplitude. The dependent variables were the number of substance dependence symptoms present and the likelihood of being diagnosed with substance dependence. Those with small P300 differed from those with large P300 by being more likely to have nicotine, alcohol, or illicit drug dependence. They were also more likely to have alcohol dependence per se and significantly more symptoms of each of these dependencies. The average amplitude group tended not to differ significantly from the small amplitude group, and for the most part, fell between the extreme groups in the proportion with dependence diagnoses and in mean symptom counts.

The psychophysiological high-risk design was applied to electrodermal response modulation in Taylor et al. (1999). Again, boys were selected from the extremes as well as the middle of the electrodermal response modulation distribution. This distribution was generated by exposing subjects to an assessment protocol called ‘coolest’ because the subject’s task is to ‘stay cool’ while anticipating a 2-s noise blast. Electrodermal mod-

ulation scores indicated the degree to which subjects responded less when the aversive sound was temporally predictable. Those with low modulation scores were unable to take advantage of stimulus predictability and actually responded with larger skin conductance responses when the stimulus was predictable than when it was unpredictable. It was hypothesized that these individuals would be especially likely to have a weak inhibitory control system, and therefore they were expected to be at high risk for substance dependence. The responses of participants with high modulation scores were stronger to the unpredictable stimuli, a finding consistent with the notion that they were able to control or inhibit their autonomic response when they knew precisely when the aversive stimulus was to occur. This group was expected to be at reduced risk for substance dependence. The results supported the hypotheses in that the two extreme groups differed significantly and in the predicted direction in their symptom counts for nicotine and alcohol but not cannabis dependence. With the exception of cannabis dependence, the ‘average’ response modulation group produced symptom counts that were intermediate to those of the other two groups.

1.3. Rationale for the present investigation

The relationship of electrodermal response modulation to P300 amplitude has not been examined. Because little is known regarding the mechanism that links either measure to putative risk for substance use disorders, one can only speculate regarding the possible link between the two. These psychophysiological measures were hypothesized by the study authors to be tapping into a dimension related to genetic risk for the development of these disorders that is characterized by dysregulation of inhibitory control (Iacono et al., 1999). The coolest task would appear to provide a direct measure of at least one type of inhibitory control because it provides a test of a person’s capacity to inhibit an autonomic response to one of two stimuli that differ only in their temporal predictability. Evidence supporting P300 as an index of inhibitory control is more

indirect and includes the fact that reduced P300 amplitude is associated with disruptive behavior disorders of childhood in MTFs adolescents (Iacono, 1998; Carlson et al., 1999; Iacono et al., 1999) and antisocial personality disorder in MTFs fathers (Malone et al., 2000). Other investigators have also noted that reduced P300 is associated with antisocial behavior, including conduct problems prior to age 15 (Bauer and Hesselbrock, 1999), impulsive aggressiveness (Branchey et al., 1988; Barratt et al., 1997) and a personal or family history of antisocial personality disorder (Bauer et al., 1994a,b). Citing the work of various investigators who have speculated that P300 positivity reflects a widely distributed inhibitory event in the brain, Begleiter and Porjesz (1999) hypothesize that the genetic predisposition to inherit alcoholism involves a state of central nervous system hyperexcitability/disinhibition that is reflected in reduced P300 amplitude. Although it may be that both psychophysiological measures reflect the presence of an inhibitory control deficit, there is as yet no reason to assume they would necessarily tap the same underlying central nervous system processes.

In the present investigation, we examined how extreme groups, defined by the intersection of the distributions of scores on P300 and electrodermal modulation, differ in substance dependence risk. Although the MTFs P300 paradigm was used with all 17-year-old boys, the version of the cool-test protocol used by Taylor et al. (1999) was available for only 150 participants. Hence, we examined how the two candidate endophenotypes defined substance dependence risk in this MTFs subsample. To simplify the presentation of the data, subjects were split into four groups using as the dividing point the median P300 target amplitude and electrodermal modulation score. It was hypothesized that subjects who fell below the median on both measures would be at extra-high risk for substance dependence while those above the median on both would be at extra-low risk. Individuals below the median on one variable but above on the other were expected to be at intermediate risk.

To explore further the notion that reduced

P300 and deficient electrodermal response modulation are indicative of an inhibitory control deficit, group differences were examined in performance on an antisaccade eye tracking task, an ocular motor test of inhibitory control. For this task, subjects fixate on a spot of light that moves abruptly and without warning to a new location. Subjects must inhibit the natural tendency to generate a saccade in pursuit of the target and instead move their eyes in the opposite direction. Performance on this task may also constitute another endophenotype for substance dependence. In MTFs 17-year-old boys, high antisaccade error rates were associated with paternal drug abuse and antisocial personality disorder, and MZ twins discordant for a substance abuse diagnosis were nonetheless concordant in their antisaccade error rates (Iacono, 1998). More recently, MTFs 17-year-old MZ twin boys have been found to show substantially higher concordance for antisaccade performance (intra-class correlation = 0.40, $N = 170$ pairs) than DZ twins (intra-class correlation = 0.05, $N = 89$ pairs), (unpublished data).

2. Method

2.1. Participants

One hundred and twenty-nine 16–18-year-old males from the MTFs served as participants in this study (mean age = 17.18, S.D. = 0.40). These young men constituted all of the participants from the sample of 150 adolescent twins and their co-twins described by Taylor et al. (1999) with valid electrodermal modulation scores who also had valid P300 data. Participants were identified from birth certificates at the Minnesota Department of Health as being members of same-sex twin pairs born in Minnesota between the years 1971 and 1978 and were contacted over the phone or by mail during their senior year in high school. Written informed consent was obtained from each participant and also from a parent or guardian if the young man was under the age of 18 years.

2.2. P300 amplitude

A detailed description of the ERP paradigm employed is provided by Katsanis et al. (1997) and Carlson et al. (1999). Electroencephalographic (EEG) activity was recorded with an electrode cap (Electro-Cap International, Inc.) from the Pz, P3, and P4 scalp sites referenced to linked earlobes. Electro-oculographic (EOG) activity was recorded via Ag/AgCl electrodes placed above the pupil and near the outer canthus of one eye. The right shin served as ground. Impedance at the scalp and reference sites was kept below 5 k Ω . EOG and ground impedance was below 10 k Ω . EEG signals were amplified 20 000 \times with a Grass Model 12A Neurodata Acquisition System and filtered with 1/2 amplitude low and high frequency filter settings at 0.01 and 30 Hz, respectively. Data were digitized over a 2000-ms epoch at a rate of 256 Hz. A 500-ms prestimulus baseline was included in this epoch.

The task used to elicit the event-related potential was a visual oddball paradigm patterned after that of Begleiter et al. (1984). Participants sat approximately 48 cm from a color computer monitor on which the stimuli were presented in a pseudorandom order. The target stimulus was an oval representing the superior view of a head depicting a nose and one ear. This design was rotated in four positions: nose up and ear on the left, nose down and ear on the left, nose up and ear on the right, and nose down and ear on the right. Participants were required to press a button on the left arm of the lab chair when shown an ear on the left side of the head, and a right button when shown an ear on the right side of the head. In the easy condition, the nose was up and accordingly the right and left ear corresponded to the right and left button on the participant's chair. However, in the difficult condition, the head appeared to be rotated so that the nose was pointed down and consequently the right and left ear appeared on opposite sides to the right and left buttons on the participant's chair.

Participants were provided with practice trials until they comprehended the task requirements and were instructed to respond accurately but as quickly as possible. Two hundred and forty trials

were presented: 160 neutral presentations consisting of a simple oval in the center of the screen, and 40 difficult (head with nose pointed down) and 40 easy (head with nose pointed up) trials. Stimuli were presented for 98 ms each with a random interstimulus interval ranging between 1 and 2 s. Clipping of either the EEG or EOG signal led to rejection and repetition of a trial.

A computer program identified the largest peak amplitude occurring between 200 and 800 ms following stimulus onset. The blink correction method of Gratton et al. (1983) was used to reduce contamination of the EEG by eye blinks and other ocular artifacts. Additionally, a 7.5-Hz low pass digital filter was applied in order to reduce high frequency contamination not eliminated by the on-line filters. A rater blind to participants' diagnoses confirmed the selected peaks for the mean target waveforms and corrected cases where a peak had been misidentified. Peaks were checked by comparing the waveform at Pz to those recorded at P3 and P4 within the 200–800-ms window. In cases where there was more than one peak of comparable amplitude, the second peak was chosen. This procedure also served to reduce the likelihood of misidentifying P200 as the P300. Latency was defined as the difference in milliseconds between the time of stimulus onset and the occurrence of the peak amplitude. Pz was chosen as the site to use for subject selection because it has frequently been the site of focus or special attention in studies of alcohol disorder risk and P300 amplitude (Begleiter et al., 1987; Steinhauer et al., 1987; Hill et al., 1988, 1995a,b,c; Polich et al., 1988; Porjesz and Begleiter, 1990; Whipple et al., 1991; Hill and Steinhauer, 1993; Steinhauer and Hill, 1993).

2.3. Electrodermal response modulation

Details of the signal recording and laboratory paradigm used to assess electrodermal response modulation are provided in Taylor et al. (1999). Participants washed their hands with Ivory brand liquid soap and had the distal phalanges of their index and ring fingers on the left and right hand swabbed with isopropyl alcohol prior to attachment of skin conductance (SC) sensors. A 0.79-cm²

area of skin was isolated on these fingertips using electrode collars (Lykken and Venables, 1971). Ag/AgCl electrodes filled with 0.5 M NaCl solution mixed in Unibase cream were affixed to these sites (Lykken and Venables, 1971). A constant potential difference of 0.5 V was maintained across the two fingers of each hand by a SC coupler of the type described by Lykken and Venables (1971). The output of this coupler was passed through DC amplifiers of the Grass model 12-A Neurodata Acquisition System. The signal was amplified $5000\times$ and filtered with a 3-Hz low pass filter.

Participants sat in the same high-backed chair used in the ERP assessment previously described. They were instructed that they would hear a series of loud, unpleasant noises over headphones and that they were to stay as cool and calm as possible in order to see if they 'have the right stuff to be an astronaut, a test pilot, or a professional athlete.' There were five 100-s. trials. On all of the trials a graphic representation of a clock face was presented on a computer monitor in front of the participant. A sweep second hand moved across the screen from 12.00 to 12.00 h again during each trial. On trials 1, 2, and 5 a red mark on the clock indicated exactly when the noise blast would occur. On the remaining two trials there was no red mark. Participants were informed that the red mark would allow them to predict the occurrence of the blast and that some trials would be unpredictable. The second hand started its sweep on the tenth second of each trial.

The noise blast was a 2-s presentation of 90-dB white noise presented binaurally. This noxious stimulus was produced by a Coulbourn white noise generator (S81-02) that also served to provide a constant background noise of 55 dB in order to mask extraneous sounds from outside the laboratory. The noxious noise blast occurred at pseudorandom times between the 25th and 75th second of each trial.

An electrodermal response modulation (ERM) score as described by Taylor et al. (1999) indexed the percent increase or decrease in skin conductance response when the stimulus was made pre-

dictable in time. The score was calculated as follows:

$$\text{ERM} = ((\text{SCR}_{\text{UP}} - \text{SCR}_{\text{P}}) / (\text{SCR}_{\text{UP}})) \times 100\%,$$

where SCR_{UP} is the mean skin conductance response in microsiemens during the unpredictable trials and SCR_{P} is the mean skin conductance response during the predictable trials. ERM scores were calculated for the right hand as in Taylor et al. (1999).

2.4. Definition of psychophysiological risk groups

Figs. 1 and 2 illustrate grand mean ERP averages and the skin conductance response values for temporally predictable and unpredictable coolest trials. The median P300 amplitude was $22.98\ \mu\text{V}$ and the median ERM score was 27.78%. Thirty-two participants were above the median of both the ERM score and P300 amplitude (designated as the low-risk group). Thirty-two young men were below the median of the ERM score, but not below the median P300 amplitude (designated the intermediate-ERM risk group), while another 32 participants had a P300 amplitude below the median value and an ERM score above the median for that variable (designated the intermediate-P300 risk group). Thirty-three adolescents were below the median of both measures (high-risk group). Fig. 3 illustrates the scatterplot of P300 amplitude by ERM score. Despite the large N and consequent power to detect a significant association, these two variables were not significantly correlated in this sample ($r = 0.15$). Because study participants were selected from a twin study, some of the subjects in a group were related to each other. However, none of the groups contained more than six twin pairs, so each of the four groups contained a minimum of 26 unrelated individuals.

2.5. Antisaccade error

For the antisaccade task, a target, consisting of

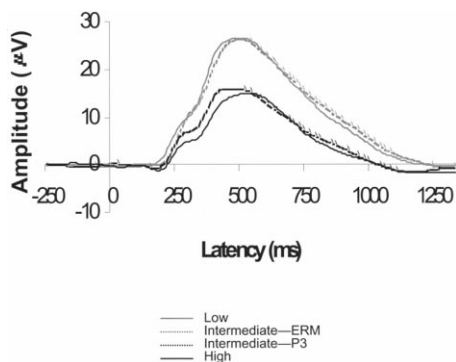


Fig. 1. Grand mean average event-related potentials at Pz for participants in each of the psychophysiological risk groups. High risk = below the median score for both psychophysiological variables; intermediate risk-P300 = below the median P300 score but above the median electrodermal response modulation (ERM) score; intermediate risk-ERM = below the median ERM score but above the median P300 score; low risk = above the P300 and ERM median scores.

a circle 0.5° in diameter, appeared in the center of a computer monitor screen that was positioned 75 cm from the subject's face. Following a 2–3-s

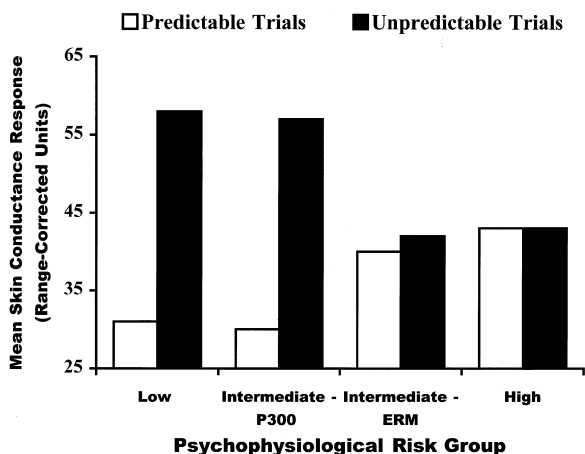


Fig. 2. Mean skin conductance response (SCR) amplitudes to coolest trials that were temporally predictable or unpredictable by psychophysiological risk group. SCRs were range corrected by dividing each participant's responses by the maximum SCR generated by that participant. High risk = below the median score for both psychophysiological variables; intermediate risk-P300 = below the median P300 score but above the median electrodermal response modulation (ERM) score; intermediate risk-ERM = below the median ERM score but above the median P300 score; low risk = above the P300 and ERM median scores.

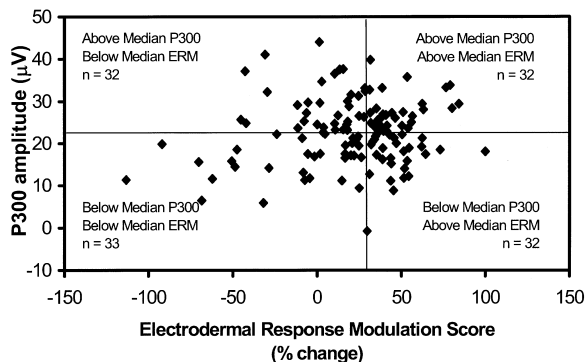


Fig. 3. Scatterplot of P300 amplitude at Pz by electrodermal response modulation (ERM) score.

pseudorandom interval, the center stimulus was extinguished and a peripheral target appeared approximately 10° either to the left or right of central fixation. Subjects, with their heads positioned in a chin rest, were told to fixate on the target when it was in the center of the screen, but to move their eyes in the direction opposite of target motion when the target moved (thus generating an antisaccade).

Data were unavailable for 10 subjects. For the remaining 119 participants, 107 were evaluated by completing an eight-trial version of the antisaccade task. The remaining 12 subjects completed a 20-trial version. For this group of 12 subjects, the Spearman correlation between performance on the first eight trials and performance on all 20 trials was 0.93, indicating that the 8- and 20-trial versions of this task were essentially interchangeable.

Ocular motion was monitored using an Eye-Trac Model 210 (Applied Science Laboratories) eye movement monitoring system that included an infra-red light source and sensors positioned in front of one eye and mounted on a head band that was adjusted to fit each subject's head. The EOG was also recorded from Ag/AgCl electrodes placed at the outer canthi and above and below one eye with a shin ground after the skin had first irritated to ensure low electrode impedance (< 10 kΩ). This recording was used to identify blinks and other artifacts that might not have been readily detectable in the infrared recording. Both the infrared and EOG recordings

were digitized online at a rate of 256 Hz. The task was scored for the proportion of errant responses, consisting of those trials where the participant glanced first in the direction of the target. Any eye movements within 100 ms of target motion were not counted because they were unlikely to have been generated in response to target movement.

2.6. Clinical assessment

Following the psychophysiological assessment participants completed structured clinical interviews conducted by individuals who had completed rigorous training in diagnostic interviewing. All interviews were audiotaped to aid in resolving ambiguous responses. A detailed description of the diagnostic procedures followed is provided in Iacono et al. (1999).

DSM-III-R criteria (American Psychiatric Association, 1987) for alcohol, nicotine, and illicit drug dependence were assessed with the expanded Substance Abuse Module (SAM, Robins et al., 1987), a supplement to the World Health Organization's Composite International Diagnostic Interview (CIDI, Robins et al., 1988). Illicit drug dependence was assessed for the following: amphetamine, cannabis, cocaine, hallucinogens, inhalants, opiates, phencyclidine, and sedatives. Participants were classified as having illicit drug dependence if they met dependence criteria for one or more of the preceding substances. Mothers of the adolescent participants were also interviewed about their sons' substance psychopathology using the parent version of the Diagnostic Interview for Children and Adolescents (DICA-R, Welner et al., 1987). This collateral information was combined with the young men's interviews in order to create best-estimate diagnoses and symptom counts (Leckman et al., 1982).

After completion of the interviews, a case review was conducted by a minimum of two senior graduate students with advanced clinical training. DSM-III-R diagnostic algorithms were then used to assign diagnoses for all of the relevant disorders. Participants were considered to have the disorder if they met either definite (all DSM-III-R criteria) or probable (all but one symptom) crite-

ria. The reliability of MTFS diagnoses following this procedure was high ($\kappa > 0.91$ for substance dependence disorders). In addition, counts of symptoms were made for the substance dependence disorders. Due to the low endorsement rate for items pertaining to illicit drug dependence in this sample, symptom counts for individual substances were combined into one drug dependence count.

2.7. Statistical analysis

The clinical dependent variables were analyzed with nonparametric statistics. The prevalence of substance dependence diagnoses was analyzed using Fisher's exact and χ^2 tests. Because most of the subjects had no symptoms of substance dependence, the symptom count data were very skewed. Hence, these data were analyzed using Mann-Whitney *U*-test and Kruskal-Wallis analysis of variance (ANOVA) as appropriate. Those in the psychophysiological high-risk group were hypothesized to be especially likely to develop substance dependence and those in the low-risk group were expected to be at especially low risk for substance use disorders. The two intermediate-risk groups defined as high on one variable and low on the other were not expected to differ from each other, but these subjects were expected to show moderately elevated risk for substance dependence. Hence, significant group comparison χ^2 and Kruskal-Wallis ANOVAs were followed with planned post hoc comparisons by determining first if the two intermediate groups differed from each other. When they did not, these two groups were combined and compared to the high- and low-risk groups, which were also compared to each other. Given the absence of differences between the two intermediate-risk groups coupled with the hypothesis of a graded clinical effect as a function of psychophysiological risk, a trend analysis was carried out to determine if the percentage of participants with a diagnosis or symptoms increased in an approximately linear fashion across risk groups. This analysis used the M^2 statistic (Agresti, 1996) which is based on the Pearson correlation and has a χ^2 distribution with one degree of freedom. Integer scores were

Table 1

Means and standard deviations for P300 amplitude, P300 latency, reaction time and hit rate during the rotating heads task, and ERM score as a function of psychophysiological risk group^a

Task Measure	Psychophysiological risk group									
	Low risk <i>N</i> = 32		Intermediate risk-P300 <i>N</i> = 32		Intermediate risk-ERM <i>N</i> = 32		High risk <i>N</i> = 33		All groups <i>N</i> = 129	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
P300 Amplitude (μ V)	28.10	4.15	17.98	3.91	29.18	5.73	16.48	4.39	22.89	7.34
P300 Latency (ms)	463.75	53.56	427.61	52.69	444.95	60.59	474.79	61.74	452.94	59.48
Reaction Time (ms) ^b	1045.41	191.14	997.00	192.26	983.00	154.02	1022.15	166.22	1012.08	176.00
Hit Rate (% correct) ^b	98.40	1.82	98.51	1.81	98.55	1.49	98.26	2.65	98.42	1.97
ERM Score (% change)	46.85	15.83	47.02	14.34	2.26	20.69	-11.83	37.93	20.82	35.72

^aHigh risk = below the median score for both psychophysiological variables; intermediate risk-P300 = below the median P300 score but above the median electrodermal response modulation (ERM) score; intermediate risk-ERM = below the median ERM score but above the median P300 score; low risk = above the P300 and ERM median scores.

^bP300 task performance data are missing for one participant.

assigned to the group variable, with 1 representing the low-risk group, 2 the collapsed intermediate risk groups, and 3 the high-risk group. A statistical test was accepted as significant if $P < 0.05$.

3. Results

Descriptive statistics for P300 amplitude, P300 latency, ERP task performance measures, and ERM score for each of the four groups and the entire sample are provided in Table 1. The four subject groups did not differ on several variables that could have affected either P300 amplitude or ERM score. There was no difference across groups in the amount of caffeine consumed prior to the lab session ($F_{3,125} = 0.10$), the number of hours slept during the preceding evening ($F_{3,125} = 0.85$), or whether participants had consumed breakfast before the laboratory session [$\chi^2(3) = 0.32$]. The proportion of subjects assessed in each of the seasons (December–February, March–May, June–August, September–November), did not differ across groups [$\chi^2(9) = 13.62$]. Further, all participants underwent the coolest procedure

between 09.00 and 10.00 h and had their ERPs recorded between 10.45 and 11.45 h. The groups did not differ significantly in either reaction time ($F_{3,124} = 0.78$) or hit rate ($F_{3,124} = 0.14$) during the rotating heads task.

3.1. Univariate median splits

To confirm that substance dependence was related both to P300 amplitude and ERM scores in this sample of 129 individuals, analyses of substance dependence prevalences and symptom counts were undertaken for each psychophysiological measure by splitting the total group at the median value for each measure. Compared to those above the median in P300 amplitude, a significantly greater proportion of participants below the median had any substance dependence (36.9% vs. 17.2, Fisher's exact test $P = 0.017$) or alcohol dependence (25.0% vs. 7.8, Fisher's exact test $P = 0.016$). The corresponding effects for illicit drug dependence (12.3% vs. 4.7, Fisher's exact test $P = 0.206$) and nicotine dependence (30.8% vs. 15.6, Fisher's exact test $P = 0.060$), although in the expected direction, did not attain statistical significance. Similarly, more of the sub-

jects with an ERM score below the median had an alcohol dependence diagnosis than those above the median value, 24.6 vs. 7.9% (Fisher's exact test $P = 0.016$). The proportion of participants with any substance dependence (33.8 vs. 20.3%, Fisher's exact test $P = 0.113$), illicit drug dependence (6.2 vs. 10.9%, Fisher's exact test $P = 0.364$) and nicotine dependence (29.2 vs. 17.2%, Fisher's exact test $P = 0.144$) did not differ significantly for those below and above the median ERM score.

The analysis of substance dependence disorder symptom counts for those above and below the P300 and ERM medians produced results that paralleled those for the diagnoses. With respect to P300, those below the median had significantly more symptoms of nicotine dependence ($U = 1754.0$, $P = 0.045$). Non-significant trends in the expected direction were evident for any substance dependence ($P = 0.065$), alcohol dependence ($P = 0.127$), and illicit drug dependence ($P = 0.530$). For ERM scores, significant effects in the expected direction were evident for any substance dependence ($U = 1609.5$, $P = 0.008$), alcohol dependence ($U = 1576.0$, $P = 0.002$), and nicotine dependence ($U = 1714.5$, $P = 0.025$), but not for illicit drug dependence ($P = 0.516$).

3.2. Bivariate median splits

The diagnosis and symptom count variables were compared for the high-risk, two intermediate-risk, and low-risk groups. The results for the substance dependence diagnoses are summarized in Fig. 4. As can be seen from the figure, as hypothesized, persons in the low-risk group were least likely to have a substance diagnosis, while those in the high-risk group were most likely to have one. Those in either intermediate-risk group had moderate rates of dependency. χ^2 tests confirmed that the four groups differed significantly for any substance dependence [$\chi^2(3) = 10.96$, $P = 0.012$] and alcohol dependence [$\chi^2(3) = 16.09$, $P < 0.001$]. Planned follow-up post hoc tests revealed that the two intermediate groups did not differ in the rate at which they had any substance dependence or alcohol dependence. When these two groups were collapsed, they did not signifi-

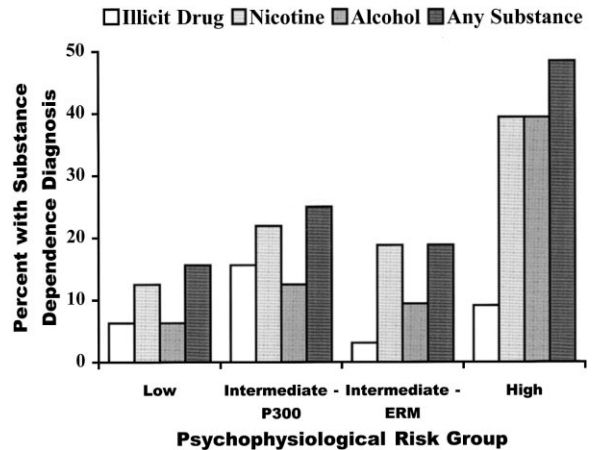


Fig. 4. Percentage of participants with illicit drug, nicotine, alcohol, and any substance dependence diagnoses in each psychophysiological risk group. High risk = below the median score for both psychophysiological variables; intermediate risk-P300 = below the median P300 score but above the median electrodermal response modulation (ERM) score; intermediate risk-ERM = below the median ERM score but above the median P300 score; low risk = above the P300 and ERM median scores.

cantly differ from either the high- or low-risk groups. The high and low risk groups did differ from each other, however, for any substance dependence ($P = 0.011$) and for alcohol dependence ($P = 0.002$). Although the trend for nicotine dependence indicated a similar effect, the resulting χ^2 test fell short of statistical significance [$\chi^2(3) = 7.29$, $P = 0.063$]. The effect for illicit drug dependence was not significant [$\chi^2(3) = 3.49$, $P = 0.322$]. To determine if the proportion of participants with a diagnosis increases linearly with increasing psychophysiological risk, those in the two intermediate risk group were collapsed into a single category (these two groups did not differ significantly for any of the four categories of substance dependence examined), and the M^2 statistic was computed. A linear trend was confirmed for any substance dependence [$M^2(1) = 8.89$, $P = 0.003$], alcohol dependence [$M^2(1) = 12.66$, $P < 0.001$], and nicotine dependence [$M^2(1) = 6.60$, $P = 0.01$]. The linear trend for illicit drug dependence was not significant [$M^2(1) = 0.16$].

Kruskal–Wallis ANOVAs were used to determine if the four groups differed on substance

dependence symptom counts (see Fig. 5). Significant results were obtained for any substance dependence [$\chi^2(3) = 10.65$, $P = 0.014$], alcohol dependence [$\chi^2(3) = 12.43$, $P = 0.006$], and nicotine dependence [$\chi^2(3) = 9.35$, $P = 0.025$], but not illicit drug dependence [$\chi^2(3) = 2.95$, $P = 0.400$]. Follow-up of the three significant findings with planned post hoc tests revealed that the two intermediate-risk groups did not differ in their symptom counts. When these groups were collapsed, they did not differ significantly from the high-risk subjects, but they did differ significantly from the low-risk group. This was so for any substance dependence ($P = 0.011$) and alcohol dependence ($P = 0.003$), but not for nicotine dependence ($P = 0.055$). In addition, adolescents in the low-risk group had fewer symptoms of dependence than those in the high-risk group for any substance dependence ($P = 0.003$), alcohol dependence ($P = 0.002$), and nicotine dependence ($P = 0.004$).

To further evaluate the hypothesis that those in the low-risk group would have less evidence of substance dependence than those in the collapsed

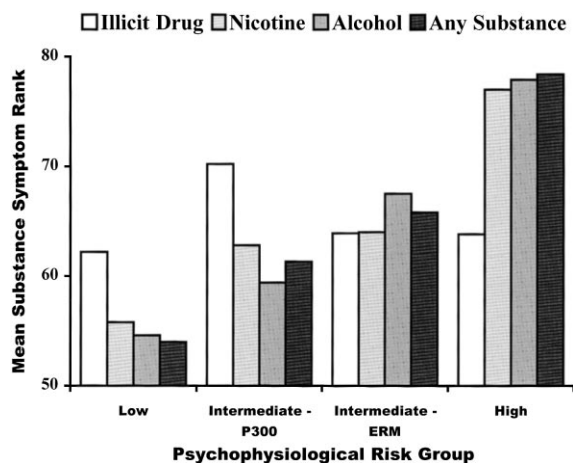


Fig. 5. Mean ranks corresponding to the substance dependence symptom counts present in each psychophysiological risk group for illicit drug, nicotine, alcohol, and any substance. High risk = below the median score for both psychophysiological variables; intermediate risk-P300 = below the median P300 score but above the median electrodermal response modulation (ERM) score; intermediate risk-ERM = below the median ERM score but above the median P300 score; low risk = above the P300 and ERM median scores.

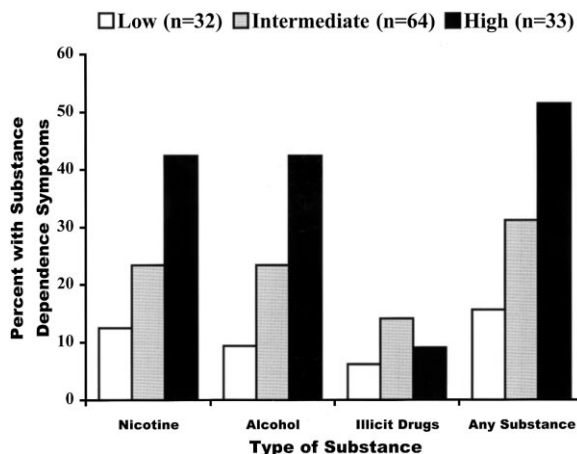


Fig. 6. Percentage of participants with varying degrees of psychophysiological risk who have at least one dependence symptom by type of substance (any substance, alcohol, illicit drug, and nicotine). High risk = below the median score for both psychophysiological variables; intermediate risk = below either only the median P300 score or the median electrodermal response modulation (ERM) score; low risk = above the P300 and ERM median scores.

intermediate-risk group, who in turn would have less than those in the high-risk group, the proportion of subjects who fell into each of these three groups who had at least one symptom of substance dependence was determined. These results are illustrated in Fig. 6 which shows that, except for illicit drug dependence, the proportion of individuals with at least one dependence symptom almost doubles as psychophysiological risk increases from low to intermediate to high. Applying the M^2 statistic to these data confirmed the presence of a linear trend for any substance dependence [$M^2(1) = 9.48$, $P = 0.002$], alcohol dependence [$M^2(1) = 9.46$, $P = 0.002$], and nicotine dependence [$M^2(1) = 7.61$, $P = 0.006$]. The effect for illicit drug dependence was not significant [$M^2(1) = 1.49$].

3.3. Antisaccade task performance

The antisaccade error rates associated with group membership are illustrated in Fig. 7. Because most subjects perform this task with few or no errors, the antisaccade error data were skewed and therefore analyzed with non-parametric

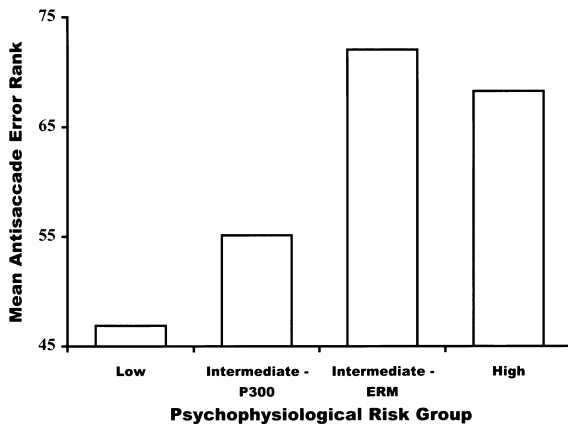


Fig. 7. Mean ranks for antisaccade error rates for each psychophysiological risk group. High risk = below the median score for both psychophysiological variables; intermediate risk-P300 = below the median P300 score but above the median electrodermal response modulation (ERM) score; intermediate risk-ERM = below the median ERM score but above the median P300 score; low risk = above the P300 and ERM median scores.

statistics. A Kruskal–Wallis ANOVA applied to these data was significant [$\chi^2(3) = 10.34$, $P = 0.016$], with follow-up tests confirming that the two groups below the median ERM score (the high-risk and intermediate-ERM groups) did not differ (their median antisaccade error score was 25%), nor did the two groups above the median ERM score (low-risk and intermediate-P300 groups; their median error score was 50%), but both groups below the median ERM score differed significantly from subjects in the low risk group (both P values < 0.02). In addition, the two intermediate groups differed from each other ($P = 0.05$). Hence, antisaccade error was associated with poor electrodermal response modulation but not reduced P300 amplitude.

3.4. Possible effects of substance use

To evaluate the likelihood that a subject's history of substance use affected his score on the psychophysiological variables, Kendall tau correlations were computed between various measures of use and P300 amplitude, ERM score, and antisaccade error rate for the entire sample. The measures of use examined were number of

lifetime alcohol intoxications, estimated alcohol consumption in the preceding 12 months, maximum alcohol consumption in 24 h, typical daily cigarette or chewing tobacco use, heaviest use of cigarettes or chewing tobacco, ever used an illicit drug, and number of lifetime uses of illicit drugs. Of the resulting correlations, the absolute value of the largest was 0.20 and the median was -0.07 . Because a diagnosis of substance dependence was correlated with these three psychophysiological measures, and it is reasonable to assume that those with these diagnoses use substances more than those without them, these correlations are surprisingly small and indicate that at best a trivial amount of the variance in the psychophysiological measures can be attributed to substance use.

4. Discussion

4.1. Summary of findings

This investigation focused on the relationship of substance dependence to psychophysiological risk in boys, most of whom were high school seniors. All were below the legal age for alcohol consumption, and most were not old enough to legally buy cigarettes. Nevertheless, many of these youths have symptoms of substance dependence, and some have satisfied criteria for DSM-III-R substance use disorders at least at the probable level. Those with clinical symptoms were disproportionately represented in the high risk group, defined by deficient electrodermal modulation and reduced amplitude P300. Individuals who were below the median on only one of these measures tended to have less DSM symptomatology, and those whose psychophysiology identified them as in the lowest risk group showed relatively little evidence of substance dependence. For any substance dependence and alcohol dependence, the high- and low-risk groups always differed significantly from each other in both the proportion of those in each group who had a substance diagnosis and in the number of DSM substance dependence symptoms. The two groups at intermediate risk for substance dependence never differed from

each other on these clinical variables, and did not differ significantly from the high-risk group in substance dependence symptom counts. The intermediate groups did differ significantly in the expected direction from the low-risk group for the symptom count variable. In addition, linear trend analyses indicated that the groups were ordered as hypothesized with respect to the presence of substance dependence diagnoses and symptoms, with the intermediate-risk subjects falling between the high- and low-risk groups. These effects were not evident for illicit drug dependence, a finding that was not surprising given the relative inexperience of 17-year-old boys with illicit substances.

4.2. Contribution of the multivariate endophenotype

These findings thus illustrate the value of using two different putative psychophysiological endophenotypes to identify risk for the development of substance use disorders. By combining the results from two measures, it was possible to identify individuals at especially high risk for substance use disorders, especially alcoholism or nicotine dependence. For instance, considering the rate at which alcoholism was diagnosed, those below the P300 median and those below the ERM median received this diagnosis at the probable or definite level approximately 25% of the time. When an individual fell below both medians, the probability of having an alcoholism diagnosis jumped to 0.39. This pattern of results was repeated for any substance dependence and nicotine dependence. Viewed from another perspective, this 39% prevalence of alcoholism in the high-risk group was over four times the rate evident in the intermediate-ERM group (9%) and three times the rate in the intermediate-P300 group (13%). It was over six times the rate evident in the low-risk group (6%). Thirty-nine percent of the high-risk group had nicotine dependence, a rate that was approximately double that of the intermediate-risk groups (which averaged 20%), and approximately three times the rate evident in the low-risk group (12.5%). Odds ratios also confirm that risk is elevated in the high-risk group when the rate of dependence diagnosis in this group is compared to the rate evident in the

remaining three groups collapsed into one. The odds ratios (together with their 95% confidence intervals) were 3.81 (1.63, 8.90), 6.28 (2.36, 16.73), and 3.02 (1.26, 7.23), respectively, for any substance dependence, alcoholism, and nicotine dependence. All of the elevated odds ratios were statistically significant, all P values < 0.02 .

4.3. P300 and disinhibition

As Fig. 3 illustrated, the two psychophysiological measures were uncorrelated. This finding, coupled with the fact that antisaccade error was associated with only electrodermal response modulation, is consistent with the notion that these two measures are tapping into different processes, both possibly reflecting a dysfunction in inhibitory control, that underlie risk for the development of substance use disorders. Reduced P300 amplitude has been associated with impulsive and externalizing behavior disorders hypothesized as sharing a common disinhibitory process in their etiologies (Gorenstein and Newman, 1980). Barratt et al. (1997) found small P300 amplitude in inmates characterized as being impulsively aggressive when they were compared to non-impulsive, but aggressive prisoners. Reduced P300 amplitude has been found in individuals with antisocial personality disorder (Bauer et al., 1994b) and a family history of antisocial personality disorder (O'Connor et al., 1994) in the absence of a family history of alcoholism. Although O'Connor et al. (1994) found reduced P300 amplitude to be associated with a family history of alcoholism independent of a family history of antisocial personality disorder, there is evidence suggesting that the relationship between alcoholism risk and reduced P300 may, in fact, be restricted to an antisocial or undersocialized subtype of alcoholism. Only alcoholics with disordered regulation of aggression, characterized as displaying Type 2 alcoholism phenotype of Cloninger (1987), had small P300 when contrasted with other alcoholics in one study (Branchey et al., 1988). Iacono et al. (1999) further found small P300 amplitude in the adolescent sons of alcoholics with antisocial tendencies, but not in the sons of socialized alcoholics. In

addition, P300 amplitude was smaller in the young men with higher scores on an index of disinhibited psychopathology. This is consistent with the findings of Carlson et al. (1999) that 61% of adolescent men in their sample with extremely small P300 had at least one externalizing disorder (i.e. conduct disorder, adult antisocial behavior, attention deficit hyperactivity disorder, or oppositional defiant disorder) compared to 29% of the those with large amplitudes. It is possible that P300 amplitude may be related to an inhibitory process unrelated to a type of neuropsychological disinhibition indicated by low ERM scores and high antisaccade task error rates. While these latter two variables may be related to a common disinhibited process, this process may represent a narrower influence on disinhibition than P300. The amplitude of P300 may be related to a broader, more global inhibitory process (see Begleiter and Porjesz, 1999, for a proposed model along these lines) which may be more likely manifested in personality dimensions related to impulsivity and externalizing disorders.

4.4. Electrodermal modulation, inhibitory control and the frontal lobes

The hypothesis that deficient electrodermal modulation is indexing a dysfunction in inhibitory control is bolstered by the association between scores on this task and antisaccade error rates. Although undoubtedly recruiting different but perhaps overlapping neural circuits, the antisaccade and electrodermal modulation tasks share two key features. The antisaccade task requires one to inhibit a 'prepotent' response, the natural tendency to follow the target with one's eyes. Since the blast of noise experienced in the two conditions of the coolest task was equally noxious but differed only with respect to whether its timing was predictable, it appears that some individuals are able to dampen, or inhibit, their normal response to the noise blast. Hence, both tasks appear to involve inhibitory control, whether over ocular movements or autonomic responses.

Both tasks also involve maintaining an appropriate anticipatory set and preparatory re-

sponses as well. Roberts et al. (1994) have argued that the ability to keep task instructions activated in working memory is at the heart of correct performance in the antisaccade task. Successful electrodermal modulation on predictable trials of coolest requires preparatory activity in anticipation of the noise blast. Damasio and colleagues have observed a deficit in anticipatory electrodermal responding among subjects with lesions of medial-orbital prefrontal cortex and suggest that medial-orbital prefrontal cortex exerts a regulatory influence on the activity of autonomic nuclei (Bechara et al., 1997). Indeed, Taylor et al. (1999) found that those who were able to take advantage of temporal predictability during coolest had a significantly greater number of anticipatory electrodermal nonspecific responses preceding the noise blasts. Anticipatory processes may 'tune' appropriate brain regions (Roland, 1985) with the aid of representational processes, thereby allowing one to maintain an appropriate task orientation in relation to the spatiotemporal context.

Many researchers have proposed that a chief function of the prefrontal cortex is to control interference and exert inhibitory control over behavior, such that extraneous stimuli can be ignored and task-irrelevant responses inhibited (e.g. Fuster, 1989; Dempster, 1992; Diamond, 1991). Consistent with this notion, patients with lesions of dorsolateral (Guitton et al., 1985; Pierrot-Desseilligny et al., 1991) and ventrolateral (Walker et al., 1998) prefrontal cortex have been observed to make a large number of direction errors on the antisaccade task. Recordings of the activity of single neurons in the supplementary eye fields suggest that neurons in this region of prefrontal cortex exert inhibitory control over reflexive saccades (Schlag-Rey et al., 1997). Imaging studies, while somewhat inconsistent, have implicated several cortical regions in antisaccade performance, including the frontal eye fields and anterior cingulate and dorsolateral prefrontal cortices (Everling and Fischer, 1998). Hence, it is tempting to speculate that the inhibitory control dysfunction underlying deviant electrodermal response modulation and high antisaccade error rates is mediated in part by the frontal cortex.

4.5. Limitations

This study is not without certain limitations. First, the psychophysiological assessment did not precede the development of substance use pathology in these adolescent boys. Hence, the possibility that substance use has colored the responses to the psychophysiological tasks cannot be ruled out. However, it seems unlikely that substance use has affected the psychophysiological measurements because various measures of substance use showed no appreciable correlation with P300 amplitude, ERM score, or antisaccade performance. Another concern stems from the fact that many of the subjects in the current investigation were related to each other, a factor that may have inflated the likelihood of finding significant effects. Although there is no generally accepted method to correct for this problem with non-parametric statistics, it is noteworthy that had a more conservative *P*-value such as 0.025 been adopted before accepting the results of a statistic as significant, it would have had little influence on the interpretation of the findings from the present investigation. In fact, only one of the statistical tests that yielded a significant finding produced a value between 0.025 and 0.05. Finally, many questions remain unanswered about the nature of the mechanism that underlies the increased vulnerability for substance dependence that exists in the high-risk group. Additional research is needed to both replicate the effects noted here and determine what factors contribute to the observed findings. Because the MTFS is a longitudinal study, it will be of interest to determine if those in the high-risk group who did not have substance dependence at age 17 are at increased risk to develop these disorders as they pass into adulthood, and whether there are variables that moderate this likelihood.

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