Biological vulnerability to alcoholism in children of alcoholics
Ratsma, J.E.

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P3 event-related potential, dopamine D2 receptor A1 allele and sensation seeking in adult children of alcoholics*

ABSTRACT

Research has indicated a close relationship between the P3 event-related potential and the dopamine D2 receptor A1 allele in individuals at high risk for alcoholism. Other research has suggested an association between the dopamine D2 receptor A1 allele and sensation seeking. In this study, we further examined the relationships between the P3, the A1 allele, and sensation seeking in a sample of nonalcoholic adult children of alcoholics. Participants (n = 57; range 19-30 years; 41 women), who performed a visual novelty oddball task to elicit the P3; were asked to fill in personality questionnaires including Zuckerman’s Sensation-Seeking Scale; and were classified according to the presence of the dopamine D2 receptor A1 allele. The effects of sex, age, and socioeconomic status were assessed to determine whether these variables affected the relations between the P3, the A1 allele, and sensation seeking. A small P3 amplitude was associated with high sensation seeking, particularly with high disinhibition. The presence of the A1 allele was also associated with high disinhibition, but only in men. By contrast, P3 amplitudes and latencies were not associated with the presence of the A1 allele. Although a small P3 amplitude, high sensation seeking and the presence of the A1 allele were all associated with alcoholism risk, these findings indicate that these three characteristics together do not reflect a common risk factor in alcoholism.

INTRODUCTION

Over the past two decades, evidence has accumulated indicating that the P300 or P3 component of the human event-related potential (ERP) may provide a vulnerability or trait marker of alcoholism [for reviews, see Porjesz et al. (1998) and Van der Stelt (1998, 1999)]. Specifically, it has been found that the size or amplitude of the P3 (a) is smaller in alcoholics than in nonalcoholic unrelated controls (Cohen et al., 1995; Pfefferbaum et al., 1991; Porjesz et al., 1998); (b) is associated with a family history of alcoholism, rather than with the amount of alcohol abused, in alcoholics (Patterson et al., 1987; Pfefferbaum et al., 1991); (c) is smaller in nonalcoholic individuals at high risk for alcoholism than in low risk controls (Begleiter et al., 1984; Hill et al., 1995; Porjesz et al., 1998; Van der Stelt et al., 1998a,b); (d) is heritable (Begleiter et al., 1998; Hill et al., 1998; Katsanis et al., 1997; Polich and Burns, 1987); and (e) is associated with alcoholism within families densely affected with alcoholism (Porjesz et al., 1998). Taken together, these results strongly indicate that the P3 index a genetic risk factor for the acquisition of alcoholism.

Dopaminergic neurotransmission may play an important role in alcohol and drug abuse (Berridge and Robinson, 1998; Nestby et al., 1999; Noble, 1996), as well as in the generation of the P3. This was inferred from the sensitivity of this ERP component to dopamine-enhancing drugs in patients with Parkinson’s disease (Stanzione et al., 1991). Moreover, an association has been reported in children between a prolonged latency (Noble et al., 1994) and a small amplitude (Hill et al., 1998) of the P3 and the presence of the A1 allele, a restriction fragment length polymorphism of the dopamine D2 receptor gene (DRD2). However, a P3-DRD2 association was not found in data from the Collaborative Study on the Genetics of Alcoholism.
Concerning the structure of the receptor, a mutation of the dopamine D2 receptor has been shown to lead to changes in the specificity of the coupling of the receptor to G-proteins (Guiramand et al., 1995). This mutation may be in linkage disequilibrium with the A1 allele and may contribute to decreased dopamine D2 receptor function. Thus, these results suggest that the link between low P3 amplitude and enhanced alcoholism risk may be mediated by alterations in brain dopaminergic function.

In addition, dopaminergic neurotransmission may be involved in sensation- and novelty-seeking behavior which, in turn, has been associated with alcohol and drug abuse (Badiani et al., 1998; Bardo et al., 1996; Cloninger et al., 1988; Hooks and Kalivas, 1995). For instance, high novelty-seeking behavior in childhood has been found to predict the early onset of alcohol abuse in young adulthood (Cloninger et al., 1988). Similarly, genetic effects have been found to influence alcohol use in adolescent twins, and these influences were suggested to be mediated by differences in sensation seeking (Koopmans et al., 1994). It has also been reported that subjects carrying the A1 allele may be more inclined to seek sensation and novelty than subjects not carrying the A1 allele (Noble et al., 1998). Similarly as for the P3, these findings suggest that the link between increased sensation-seeking characteristics and enhanced alcoholism risk could be mediated by genetically influenced variation in brain dopaminergic function.

In general, interindividual differences in personality characteristics seem to have only little effect on the P3 (Polich, 1991). However, the P3 does seem to index the extremes of certain personality traits (Polich, 1991) and has also been linked to psychopathological conditions characterized by
aggression and other disinhibited behaviors (Bauer and Hesselbrock, 1999; Branchey et al., 1988; Carlson et al., 1999). These data, in conjunction with the results reviewed previously, indicate that the P3, DRD2 polymorphism, sensation-seeking characteristics, and alcoholism risk are closely related. That is, a small P3, the presence of the A1 allele, and high sensation seeking may reflect a common risk factor in alcoholism. To our knowledge, no study has yet assessed the relations of these potential risk factors within one sample of subjects. Therefore, in this study we examined the relations between the P3, DRD2 polymorphism, and sensation-seeking in greater detail in a sample of nonalcoholic young adult children of alcoholics (COAs).

**METHODS**

*Study Population*

Participants consisted of 61 adult (COAs). Forty subjects responded to advertisements, 15 subjects were recruited from children of Alcoholics Anonymous members, and 6 subjects entered the study as the relative of another participant. Of the 61 adult COAs, four were excluded: one after technical problems during electroencephalogram (EEG) registration, and three for reasons of physical ill health. The study sample therefore comprised 57 people (41 women, 16 men) with a mean age of 24.4 ± 3.1 years (range 19.0 - 30.9 years). The participants came from 49 families with one or both parents having an alcohol dependence or alcohol abuse, according to DSM-IV and the Feighner Research Diagnostic Criteria (Feighner et al., 1972). To control for possible fetal alcohol effects in the participants, maternal alcoholism was assessed, according to the same diagnostic criteria. One woman and one man were non Caucasian. The participants were physically healthy, did not currently use centrally acting
medication, and had no history of a neurological disease. History of physical health was assessed with a health questionnaire, according to our studies in younger COAs (Ratsma et al., 1999; Van der Stelt et al., 1998a).

A face-to-face interview was held with each participant. These interviews focused on: (a) lifetime alcohol and drug use, as assessed by the European Addiction Severity Index of Kokkevi and Hartgers (1995) and by the Dutch Expectancy Questionnaire of Wiers et al. (1997), and psychopathology was assessed with the Symptom Checklist-90 (SCL-90) of Derogatis (1977). In cases in which the participant reported having used at least five standard units of alcohol on one occasion, twice during the last month, or having used alcohol at least 3 days per week for at least six months, the alcohol subscale of the Composite International Diagnostic Interview (Robins et al., 1988) was used to assess possible alcohol dependence or abuse. One person had experienced a past alcohol dependency but had been in remission for more than 5 years. Four others had abused alcohol, three of whom were in remission: two for 4 years, and one for half a year. Excluding these five study subjects with alcohol-related problems had no affect on the conclusions of our results, so they were retained in the study population. The study was approved by the Medical Ethical Committee of the Academic Medical Center of the University of Amsterdam.

Genotyping

The A1 allele was identified on the dopamine D2 receptor gene with TaqI digestion (Grandy et al., 1989). Samples of all 57 participants were genotyped for the TaqI A1/A2 allele by using standard restriction fragment length polymorphism techniques (Grandy et al., 1989). Each participant
provided 8 mouth swabs according to the protocol of the high-yield noninvasive human genomic DNA isolation method (Meulenbelt et al., 1995). This yielded 16 μg DNA per individual. The primers 5014 and 971, synthesized by Eurogentec, were used to amplify a 310 base pair (bp) fragment that spanned the polymorph TaqI A site of the dopamine D2 receptor gene (Grandy et al., 1989). Amplification according to the protocol (Noble et al., 1994) was carried out in 25-μl reactions with 50 ng DNA in a standard reaction cocktail with 10 polymerase chain reaction buffer (Boehringer) with 1.5 mM MgCl (pH 8.3) and 1 unit of Taq DNA polymerase. The DNA was amplified in 36 cycles with an annealing step at 55°C for 2 minutes. The 25-μl reaction sample was digested with 10 units of TaqI restriction enzyme at 65°C for 1 hour. The obtained product was analyzed by gel electrophoresis in a 2% low melting point agarose gel containing ethidium bromide. The fragments of 310, 180, and 130 bp were visualized under ultraviolet light; the A1/A1 genotype showed an uncleaved 310 bp fragment and the A2/A2 genotype showed two fragments of 180 and 130 bp (Fig. 1). A dichotomous group (A1 or A2) variable was used for these data analyses. The A1 group included 2 A1/A1 genotypes and 30 A1/A2 genotypes. The sample characteristics are given in Table 1. The A1 (n = 10 men, n = 22 women) and A2 (n = 6 men, n = 19 women) groups did not differ significantly with respect to sex. There were no significant differences between either A1 and A2 groups or men and women in terms of age, socioeconomic status (SES), Standard Progressive Matrices test (Raven et al., 1992, 1993) or SCL-90 score. SES was assessed on a seven-step scale, according to level of education; a higher score represents a higher level of education. The general intellectual ability of each subject was estimated with
Standard Progressive Matrices; a higher score indicates more intelligence. A higher SCL-90 score represents more psychopathological symptoms. As expected, a significant sex difference, but no group (A1 or A2) difference, was present in the number of standard drinks during the last month: $F(1,56) = 7.36, p < 0.010$

![Electrophoresis Image]

Fig 1. A1 and A2 alleles separated in a 2% low melting point agarose gel by electrophoresis. M, marker; lanes 1 and 2, A1/A2 heterozygotes; lanes 3 and 4, A1/A1 homozygotes; P, A2/A2 homozygotes; N, negative control.
Table 1. Sample Characteristics for Group (A1 or A2) and Sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A1</th>
<th>Group A2</th>
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<td>25.3 3.1</td>
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<td>24.0 2.8</td>
<td>23.3 2.8</td>
</tr>
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<td>4.4 1.0</td>
<td>4.4 .9</td>
</tr>
<tr>
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<td>2.8 .9</td>
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<td>2.8 .9</td>
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<td>Standard drinks last th (raw score)</td>
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<td>13.4 11.3</td>
<td>23.5 43.4</td>
<td>45.5 35.7</td>
<td>20.0 21.3</td>
<td>26.1 27.0</td>
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<td>SCL-90 (total raw score)</td>
<td>142 47</td>
<td>130 30</td>
<td>133 36</td>
<td>127 32</td>
<td>131 39</td>
<td>130 37</td>
</tr>
</tbody>
</table>

Group A1, A1/A1 and A1/A2 genotypes; Group A2, A2/A2 genotypes; SPM, Standard Progressive Matrices test

**Personality Questionnaires**

Subjects were asked to fill in personality questionnaires, including a Dutch translation (Feij and Van Zuilen, 1984), of the Sensation-Seeking Scale (Zuckerman, 1971) and the Five-Factor Personality Inventory (FFPI) (Hendriks et al., 1999). The sensation-seeking score was represented by the total score divided by the number of items of the four subscales of the Sensation-Seeking Scale: Disinhibition (12 items), Thrill and Adventure-Seeking (12 items), Experience-Seeking (14 items), and Boredom Susceptibility (13 items). Data were analyzed with the raw scores of these scales.
Experimental Paradigm

A visual novelty oddball task (Van der Stelt et al., 1998a) was used to elicit the ERPs. In this task, subjects were exposed to three types of stimuli, referred to as nontarget and target stimuli (counterbalanced letter “O” or “X”), and novel stimuli (unique colorful abstract patterns). These stimuli were randomly delivered on a monitor, for the duration of 100 ms at a fixed rate of one per 1300 ms. The participants were instructed to press a button with the right index finger in response only to the target stimuli. They were instructed to respond as quickly as possible while maintaining a low error rate. After one block of practice, including nontarget (88%) and target (12%) stimuli, four blocks of experimental trials were presented, including nontarget (76%), target (12%), and novel (12%) stimuli. Subjects were not informed that the novel stimuli would be presented. By use of this paradigm, both the P3 elicited actively by the task-relevant, target stimuli and the P3 elicited passively by the irrelevant, attention-capturing novel stimuli could be assessed. Behavioral performance measures consisted of the speed of target detection (reaction time), the number of targets missed (misses), and the number of incorrect responses (false alarms). Only reaction times occurring between 150 and 1000 ms after the onset of the target stimulus were accepted as correct detections.

Electrophysiological Recording

The EEG was recorded at midline frontopolar (Fpz), frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz) scalp locations. The right mastoid served as reference, in accordance with prior studies (e.g. Courchesne et al., 1975; Van der Stelt et al., 1998a). Bipolar recordings of horizontal and vertical electro-oculograms were made with electrodes placed at the outer
canthi of both eyes and above and below the right eye, respectively. EEGs and electro-oculograms were digitized at 200 Hz, amplified with a filter bandpass of 0.16 to 40 Hz, and stored on a computer disk for off-line processing and analysis.

Data Analysis of Personality Questionnaires
A multivariate analysis of covariance (MANCOVA) was performed on the total sensation-seeking score and the four subscales of the Sensation-Seeking Scale. Another MANCOVA was performed on the five factors of the FFPI, both MANCOVAs had group (A1 or A2) and sex as between-subject factors. Because SES and age might be important moderating background variables, correlations were assessed between these variables and the dependent variables of the Sensation-Seeking Scale and the FFPI. When relations were significantly present, then these variables were used as covariates in the MANCOVAs. Because sex was used as an independent variable in the MANCOVAs, it was not entered as a covariate in both analyses. Follow-up tests were assessed by using Bonferroni-adjusted significance levels. Correlations between the Sensation-Seeking Scale and the FFPI were assessed.

Electrophysiological Data Analysis
To assess the quality of the performance of the visual novelty oddball task, separate ANOVAs, including group (A1 or A2) and sex as between-subject factors, were performed to analyze the behavioral data. Trials excluded from analysis of the electrophysiological data consisted of trials with incorrect behavioral responses (as defined previously), the first five trials of each block, and trials in which the EEG exceeded 100μV. Ocular artifact in the
EEG was estimated and corrected for by regression analysis in the frequency domain (Woestenburg et al., 1983). Subsequently, averaged stimulus-locked ERPs were computed at each scalp location separately for the nontarget, target, and novel stimulus. The P3 amplitude was quantified by computing the mean voltage over the 350 to 450 ms post-stimulus latency range\(^1\), by using 100 ms pre-stimulus samples as baseline. The P3 latency was assessed by determining the latency of the largest voltage value within the 300 to 800 ms post-stimulus latency range. Two types of analyses were then performed (see also Van der Stelt et al., 1998a): an analysis of the scalp topographic profile of the P3 amplitude across the five midline locations, and conventional analyses of the P3 amplitude and latency at Pz, where P3 is typically maximal. The first type of analysis involved a MANOVA, including group (A1 or A2) and sex as between-subject factors, and stimulus type (nontarget, target, novel) and scalp location (Fpz, Fz, Cz, Pz, Oz) as within-subject factors, to assess differences between group A1 and A2, and between men and women, in the scalp topographic profile of the P3 amplitudes across the midline locations. The second type of analyses involved two MANOVAs, including group (A1 or A2) and sex as between-subject factors and stimulus type (nontarget, target, novel) as a within-subject factor. Follow-up tests were assessed by using Bonferroni adjusted significance levels.

\(^1\) In addition to area measures for the estimation of the P3 amplitude, a base-to-peak amplitude method was used; the peak was defined as the largest voltage value in the 300-800 ms post-stimulus latency range. Strong correlations were found between the area and peak measures of the P3 amplitude at Pz to target \((r = 0.96)\) and novel \((r = 0.94)\) stimuli. Accordingly, the base-to-peak amplitude method yielded essentially the same results as the results based on area measures reported herein.
Correlations were presented between the P3 and the sensation-seeking scale, and also between the P3 and the FFPI, to investigate the specificity of the investigated relation between the P3 and sensation-seeking.

When SES, age, or sex had a significant effect on the dependent P3 variables, then SES, age or sex were treated as covariates; however, they were not entered in the MANOVA, but were entered in sequential multiple regression analyses that were performed on the P3, to report first the uncontrolled findings of the MANOVAs and then to report how these findings were changed after controlling for confounders. The partial correlations of the sequential regression analyses are reported. Values are reported as mean ± SD, unless stated otherwise.

RESULTS

Personality Data

The personality data are summarized in Table 2. Because SES had a significant influence on the total sensation-seeking score \(r = 0.31, p < 0.030\), and on disinhibition \(r = 0.35, p < 0.009\), SES was entered as covariate in the MANCOVA on the Sensation-Seeking Scale.

The MANCOVA revealed a main effect of sex \([F(4,49) = 5.48, p < 0.002]\); however, there was also a two-way interaction of group (A1 or A2) x sex \([F(4,49) = 3.08, p < 0.025]\). After adjustment for multiple tests, the two-way interaction of group x sex was explained only by an effect on disinhibition \([F(1,56) = 7.95, p < 0.008]\). The A1 group had higher disinhibition scores than the A2 group, but only in men.

Because SES had an effect on extraversion (FFPI1; \(r = -0.28, p < 0.040\)) and age had an effect on Agreeableness (FFPI2; \(r = -0.29, p < 0.030\)) and Emotional Stability (FFPI4; \(r = -0.43, p < 0.002\)), SES and age were entered
as covariates in the MANCOVA on the FFPI. The MANCOVA showed no significant effects of group or sex.

With regard to the Sensation-Seeking Scale and FFPI, significant correlations were observed between Total Sensation-Seeking and Autonomy (FFPI5; $r = 0.31$, $p < 0.020$), Thrill- and Adventure-Seeking and Emotional Stability (FFPI4; $r = 0.28$, $p < 0.040$), and Thrill- and Adventure-Seeking and Autonomy (FFPI5; $r = 0.31$, $p < 0.030$). No other significant correlations were found between the Sensation-Seeking Scale and the FFPI.

Table 2. Personality Data for Group (A1 or A2) and Sex

<table>
<thead>
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<td>30.3 5.9</td>
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<td>32.4 7.3</td>
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<td>37.9 9.9</td>
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<td>38.4 6.6</td>
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<td>Total Sensation Seeking (raw score)</td>
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FFPI1, Extraversion; FFPI2, Agreeableness; FFPI3, Conscientiousness; FFPI4, Emotional Stability; FFPI5, Autonomy.
**Behavioral Performance Data**

The quality of the performance of the visual novelty oddball task was adequate; only four targets were missed and there were only seven incorrect responses. A significant difference was observed in reaction time between men (302 ± 52 ms) and women (336 ± 49 ms), irrespective of group \[F (1,56) = 5.74, p < 0.030\]. Age also correlated with reaction time \((r = 0.55, p < 0.001)\) and with the number of incorrect responses \((r = -0.28, p < 0.040)\), irrespective of group and sex. The Sensation-Seeking Scale, the FFPI, and SES did not influence the behavioral measures.

**Electrophysiological Data**

For each group, the grand mean ERPs elicited by nontarget, target, and novel stimuli at each of the five scalp locations are presented in Figure 2. The MANOVA on the scalp topographic profile of the P3 amplitudes revealed that in each group, the infrequent target and novel stimuli elicited a larger amplitude P3 than did the frequent nontarget stimuli \[F (2,54) = 168.54, p < 0.001\]. In addition, by using normalized P3 amplitude data, topographic differences were found between the target P3 and novelty P3 across the midline; the novelty P3 was more dominant on the frontal and central locations, and less dominant occipitally, than the target P3 [stimulus type x location: \(F (4,53) = 18.97, p < 0.001\)]. As may be seen in Figure 2, the A1 and A2 subjects manifested differences in the P3 amplitude at Oz. However, these group differences did not exceed the post-hoc adjusted significance level, and these amplitude differences were also confounded by between-group differences in age, which affected the P3 at Oz \((r = -0.28, p < 0.040)\). When the effect of this variable on the P3 amplitude at Oz was statistically controlled, the A1 and A2 differences did not approach the level of
significance. The means of target and novelty P3 amplitude and latency at Pz are presented for group and sex in Table 3. The MANOVA on the P3 at Pz revealed no group (A1 or A2) effect, however a main effect of sex was present on the target P3 amplitude at Pz \( [F(1,56) = 6.88, p < 0.020] \), on the novelty P3 amplitude \( [F(1,56) = 5.04, p < 0.030] \), and on the novelty P3 latency \( [F(1,56) = 7.19, p < 0.020] \), but not on the target P3 latency. Thus, no significant differences between the A1 and A2 groups were observed in the P3 latency, amplitude, and scalp topography. The target P3 amplitude at Pz correlated significantly with SES \( (r = -0.32, p < 0.020) \) but not with age. The novelty P3 amplitude correlated both with SES \( (r = -0.31, p < 0.020) \) and with age \( (r = -0.36, p < 0.007) \). Finally, a correlation was observed between the novelty P3 latency and age \( (r = 0.32, p < 0.020) \). No significant correlations were found between the target P3 latency and age or SES.

![Fig 2. Grand mean ERPs, superimposed for each of the groups (A1 and A2), elicited by nontarget (left), target (middle), and novel stimuli (right).](image-url)
Table 3. P3 Amplitude and Latency for Group (A1 or A2) and Sex

<table>
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<th>Variable</th>
<th>Group A1</th>
<th></th>
<th>Group A2</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male Mean SD</td>
<td>Female Mean SD</td>
<td>Total Mean SD</td>
<td>Male Mean SD</td>
<td>Female Mean SD</td>
<td>Total Mean SD</td>
</tr>
<tr>
<td>Target P3 amplitude (microvolt)</td>
<td>14.56.4</td>
<td>21.36.2</td>
<td>19.26.9</td>
<td>18.58.8</td>
<td>21.96.6</td>
<td>20.27.3</td>
</tr>
<tr>
<td>Novelty P3 amplitude (microvolt)</td>
<td>17.26.6</td>
<td>20.46.1</td>
<td>19.46.4</td>
<td>17.23.9</td>
<td>21.77.2</td>
<td>20.47.0</td>
</tr>
<tr>
<td>Target P3 latency (msec)</td>
<td>373 31</td>
<td>367 26</td>
<td>369 28</td>
<td>344 24</td>
<td>366 27</td>
<td>365 28</td>
</tr>
<tr>
<td>Novelty P3 latency (msec)</td>
<td>371 40</td>
<td>380 23</td>
<td>377 29</td>
<td>339 32</td>
<td>378 24</td>
<td>373 30</td>
</tr>
</tbody>
</table>

Relationships Between the P3 and Personality Data

A correlation was found between the target P3 amplitude at Pz and sensation seeking ($r = -0.41$, $p < 0.003$), particularly disinhibition ($r = -0.53$, $p < 0.001$) (Fig. 3). A main effect of sex was also present on the target P3 amplitude [$F (1,56) = 6.88$, $p < 0.020$] (Table 3). When the main effect of sex was controlled, the correlation between target P3 amplitude and sensation seeking remained significant [$pr = -0.34$, $F (1,54) = 6.93$, $p < 0.020$], and after controlling for SES, this relation remained significant [$pr = -0.34$, $F (1,54) = 7.24$, $p < 0.010$]. Likewise, when sex was controlled, the correlation between target P3 amplitude and disinhibition remained significant [$pr = -0.42$, $F (1,54) = 11.88$, $p < 0.005$], and after controlling for SES, this relation remained significant [$pr = -0.45$, $F (1,54) = 15.51$, $p < 0.001$]. The novelty P3 amplitude at Pz also correlated with sensation seeking ($r = -0.29$, $p < 0.050$) and with disinhibition ($r = -0.38$, $p < 0.005$). A main effect of sex was present on the novelty P3 amplitude [$F (1,56) = 5.10$, $p < 0.030$] (Table 3). After controlling the sex effect, the correlation between
novelty P3 amplitude and disinhibition remained significant \( pr = -0.27, F(1,54) = 4.34, p < 0.050 \), and after controlling for SES \( pr = -0.30, F(1,54) = 5.38, p < 0.030 \) and age \( pr = -0.35, F(1,54) = 7.40, p < 0.010 \) this relation remained significant. (Fig. 3). However, the correlation between novelty P3 amplitude and sensation seeking disappeared after controlling the sex effect. There were no other significant correlations between the P3 and the personality data (Table 4).
Fig 3. Scatterplot and regression line with the $R$ square (Rsq) in the lower right corner, presenting the negative correlations between the target P3 amplitude and sensation seeking, the target P3 amplitude and disinhibition, and the novelty P3 amplitude and disinhibition.
Table 4. Correlations between P3 Amplitudes, Latencies and Personality Data

<table>
<thead>
<tr>
<th></th>
<th>Target P3 amplitude</th>
<th>Novelty P3 amplitude</th>
<th>Target P3 latency</th>
<th>Novelty P3 latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sensation seeking</td>
<td>-0.41**</td>
<td>-0.29*</td>
<td>-0.12</td>
<td>0.05</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>-0.53**</td>
<td>-0.38**</td>
<td>-0.14</td>
<td>-0.12</td>
</tr>
<tr>
<td>Thrill and adventure seeking</td>
<td>-0.16</td>
<td>-0.06</td>
<td>-0.15</td>
<td>-0.01</td>
</tr>
<tr>
<td>Experience seeking</td>
<td>-0.18</td>
<td>-0.20</td>
<td>-0.03</td>
<td>0.11</td>
</tr>
<tr>
<td>Boredom susceptibility Extraversion</td>
<td>-0.19</td>
<td>-0.13</td>
<td>-0.01</td>
<td>0.09</td>
</tr>
<tr>
<td>Agreeableness (FFPI2)</td>
<td>0.02</td>
<td>0.19</td>
<td>-0.16</td>
<td>-0.09</td>
</tr>
<tr>
<td>Conscientiousness (FFPI3)</td>
<td>0.11</td>
<td>0.08</td>
<td>-0.11</td>
<td>-0.02</td>
</tr>
<tr>
<td>Emotional stability (FFPI4)</td>
<td>0.07</td>
<td>0.02</td>
<td>-0.07</td>
<td>-0.01</td>
</tr>
<tr>
<td>Autonomy (FFPI5)</td>
<td>-0.03</td>
<td>0.20</td>
<td>0.01</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

* p < 0.050, ** p < 0.005

**DISCUSSION**

This study found an association between a small P3 amplitude and high sensation seeking, specifically high disinhibition. Moreover, an association seemed to exist between the presence of the A1 allele and high disinhibited behavior, but only in men.

A number of studies have indicated relationships between a low P3 amplitude and behavioral disinhibition [see the review by Begleiter and Porjesz (1999)]. For instance, a significant inverse correlation has been reported in children between the P3 amplitude and externalizing problem
behavior (Van der Stelt et al., 1998a), indicating aggression and delinquency as assessed by parental ratings. Data from the Minnesota Twin Family Study have also shown that a lower P3 amplitude is associated with externalizing psychopathology and alcohol dependence in males aged 16 to 18 years (Carlson et al., 1999). In addition, a lower P3 amplitude was related to a disordered regulation of aggression in alcoholics (Branchey et al., 1988). Consistent with these findings, these data show a relationship between a small P3 amplitude and high sensation-seeking behavior, particularly disinhibition. Given the association between sensation seeking and alcoholism risk (Bardo et al., 1996; Cloninger et al., 1988), these findings together with prior findings indicate that the association between a low P3 and increased alcoholism risk can be partly explained by disinhibited behavior.

This study did not reveal a significant association between the P3 and the A1 allele. An association has been described in children at high risk for alcoholism between a prolonged latency (Noble et al., 1994) and a smaller amplitude (Hill et al., 1998) of the P3 and the presence of the A1 allele. Our findings do not seem to be consistent with these studies. This apparent discrepancy may be due to the fact that the A1 allele is not a functional mutation and does not span a coding area on the dopamine D2 receptor gene (Gejman et al., 1994), although a functional allelic variant in a regulatory region, in linkage disequilibrium with the A1 allele, may affect the receptor expression (Noble, 1996; Noble et al., 1991). Thus, differences in study results may be based on differences in subject samples concerning the level of linkage disequilibrium between the A1 allele and a functional mutation in the dopamine D2 receptor gene or in a regulatory region. Also, in contrast to the studies of Noble et al. (1994) and Hill et al. (1998), our study included
more women than men. Because the differences in P3 amplitudes between the A1 and A2 groups tended to be larger in men than in women (Table 3), this sex difference could explain the apparent discrepancy between this study and previous studies. Our results, however, are consistent with the results of the Collaborative Study on the Genetics of Alcoholism, in which no relation was found between the P3 and the presence of the A1 allele in young adults (Begleiter et al., 1998).

In this study, no significant differences between target and novel stimuli were noted in the P3 amplitude at Pz. In contrast, previous studies with a visual novelty oddball paradigm have found that the target P3 is typically larger at Pz than the novelty P3 (e.g. Courchesne et al., 1975; Van der Stelt et al., 1998a). The reason for the difference between the current and prior findings is not clear, but it could be the case that the novel stimuli, although not the target stimuli, elicited a fairly large P3 at Pz in this sample of high-risk subjects. Indeed, significant differences between young COAs and low risk controls have been noted in the amplitude at Pz of the target P3, but not in that of the novelty P3 (Van der Stelt et al., 1998a). In this high risk sample, the elicitation of a low, abnormal target P3 and a large, normal novelty P3 at Pz might have obscured the P3 amplitude differences typically observed between target and novel stimuli at this scalp location. Nevertheless, consistent with typical observations in novelty oddball paradigms (e.g. Courchesne et al., 1975; Van der Stelt et al., 1998a), the analyses on the normalized P3 amplitude data in this study did reveal topographic differences between the target P3 and novelty P3 across the midline.

This study revealed an association between the presence of the A1 allele and disinhibited behavior, but only in men. The interaction between sex and
A1 on disinhibition was unexpected, because to our knowledge no previous studies have reported such an interaction. Our study aimed to investigate the relationship between the P3, the A1 allele and sensation-seeking behavior. Although we expected to find a relation between the P3 and sensation seeking, this may be a false positive finding, because we performed multiple tests to investigate the specificity of the reported relationship.

In conclusion, this study shows a relationship between a small P3 amplitude and high sensation-seeking behavior, particularly high disinhibited behavior, a relationship between the presence of the A1 allele and high disinhibited behavior, but only in men. Although a small P3 amplitude, high sensation-seeking, and the presence of the A1 allele are all associated with alcoholism risk, our findings indicate that these three characteristics do not together reflect a common risk factor in alcoholism.
REFERENCES


Feij JA, Van Zuilven RW (1984) De Spanningsbehoefstelijst (SBL) [The Dutch Version of Zuckerman’s Sensation-Seeking Scale, Form IV]. Swets & Zeitlinger, Lisse, the Netherlands.


