Path Analysis of P300 Amplitude of Individuals from Families at High and Low Risk for Developing Alcoholism

Shirley Y. Hill, Huixing Yuan, and Jeannette Locke

Background: *A substantial amount of evidence exists suggesting that P300 amplitude in childhood is a risk marker for later development of alcohol dependence. There is evidence that P300 amplitude is heritable. The goal of the present study was to determine if patterns of transmission differed in families who were either at high or low risk for developing alcohol dependence.*

Methods: *Auditory P300 was recorded from 536 individuals spanning three generations. The path analytic TAU model was used to investigate the familial transmission of P300 amplitude in the two independent samples of families.*

Results: *Transmission of P300 in high-risk families most likely followed a polygenic model of inheritance with significant parent-to-offspring transmission. Parent-to-offspring transmission was significantly greater in high-risk than low-risk families. Total phenotypic variance due to transmissible factors was greater in low-risk families than in high-risk families, however. A somewhat unexpected finding was the substantial correlation between mates for P300 amplitude in both high- and low-risk families.*

Conclusions: *P300 is transmissible in families. Differences exist in the pattern of transmission for P300 in families at high and low risk for alcoholism.* Biol Psychiatry 1999;45:346–359 © *1999 Society of Biological Psychiatry*

Key Words: P300, high risk, TAU model, familial transmission, personality, path analysis

Introduction

The possibility that the P300 component of the event-related potential (ERP) may have etiological significance for the development of alcoholism has been discussed for nearly two decades (Pfefferbaum et al 1979; Begleiter et al 1984; Steinhauer et al 1987). These early studies suggested that both alcoholic and nonalcoholic individuals with a family history of alcoholism exhibit dysfunction in information processing. More recent studies continue to point to differences in P300 in high-risk minor children (Hill and Steinhauer 1993a; Steinhauer and Hill 1993; Hill et al 1995a, 1995c; Berman et al 1993) who had not begun to use alcohol or other substances, augmenting the argument that P300 is a risk marker for later development of alcohol dependence and not merely a state marker for recent use of alcohol or an indicator of alcohol-related cognitive deficits.

The alteration in information processing seen in these individuals is most probably the result of differences in attentive information processing. The P300 component of the ERP is a scalp-positive waveform that occurs approximately 300 msec after an informative event that is part of an active task. Production of the P300 component is thought to be closely linked to the stimulus information presented and the subject's attention to that information (Donchin 1979; Donchin et al 1978; Pritchard 1981; Sutton and Ruchkin 1984).

Whether the P300 amplitude remains a marker for alcohol dependence into adulthood is not clear. Differences in the amplitude of P300 of adult abstinent male alcoholics in comparison with normal controls have been reported in some studies (Pfefferbaum et al 1991; Porjesz et al 1987a, 1987b), but not in all of them (Pfefferbaum et al 1979; Steinhauer et al 1987; Lille et al 1987; Hermanutz et al 1981; Hill et al 1995b). Therefore, we have speculated that normalization of the differences observed between high- and low-risk children probably occurs sometime in adulthood for males. While P300 amplitude in childhood may be a marker for later development of alcoholism in adulthood, there may be too many extraneous factors (e.g., alcohol and drugs, environmental influences) altering brain functioning for P300 to be measured during adulthood and provide reliable assessment of risk. Elucidating the factors influencing the P300 component, particularly heritable factors, is of interest given the

From the Alcoholism and Genetics Research Program, University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania (SYH, JL); and Naval Health Research Center, San Diego, California (HY).

Address reprint requests to Shirley Y. Hill, PhD, University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213.

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observed associations of the P300 component with psychological dysfunction, including the predisposition to develop alcohol dependence.

There is ample evidence that brain electrical activity is heritable, including background electroencephalogram (Young et al 1972; Vogel et al 1979; Propping et al 1980; Lykken et al 1974), averaged sensory evoked responses (Buchsbaum 1974; Rust 1975), or event-related potential characteristics (Bock 1976; Surwillo 1980; Polich and Burns 1987; Steinhauer et al 1987; Rogers and Deary 1991). When one compares the overall shape of ERP waveforms of two individuals, greater concordance can be observed between siblings than unrelated individuals, with the greatest similarity being seen between twins (Steinhauer et al 1987). Similarity of ERP components in monozygotic twins has been noted in a number of studies (Bock 1976; Surwillo 1980; Polich and Burns 1987; Rogers and Deary 1991; O'Connor et al 1994; van Beijsterveldt 1996), with quantitative estimates of heritability being provided by some (O'Connor et al 1994; van Beijsterveldt 1996).

Similarities between sibling pairs have also been reported previously. Steinhauer et al (1986) studied 12 pairs of adult siblings (mean age 34.7 years), using an auditory procedure to elicit ERPs and finding substantial correlations in P300 amplitude between siblings; however, analysis of P300 latency in the same subjects revealed negligible correlations. Segregation analysis of P300 gave evidence for a major gene effect (Aston and Hill 1990). Lack of correlations in latency have also been noted in twins by O'Connor et al (1994) and van Beijsterveldt (1996). Thus, the likelihood of P300 latency having a significant genetic component is highly unlikely.

The lack of significant familial correlations in P300 latency may not be surprising in view of the substantive extant literature demonstrating the relationship between organic brain dysfunction and increased latency of P300 (Goodin et al 1979; Neshige et al 1988; Papanicolaou et al 1984; Polich 1989, 1991; Polich et al 1990). Patients with dementia often exhibit P300 latency in excess of 400 ms in auditory tasks (Neshige et al 1988). This may be contrasted with decreased amplitudes that are typically observed in psychopathological conditions such as schizophrenia (Steinhauer and Zubin 1982; Steinhauer et al 1991; Pfefferbaum et al 1989).

Although quantitative estimates of heritability of P300 amplitude have been reported (O'Connor et al 1994; van Beijsterveldt 1996) based on analysis of twin data, to date there have not been any published studies reporting quantitative estimates based on family data. Therefore, the present study focuses on within-family variation in P300 amplitude elicited from an auditory event-related potential task. In that task, subjects are asked to determine if a tone is a "target" or a "nontarget," based on the pitch (high-frequency tones are targets and low-frequency tones are nontargets). While the present data have been analyzed extensively to determine possible differences between high- and low-risk groups (Hill and Steinhauer 1993a, 1993b; Hill et al 1995a, 1995b, 1998), the goal of this analysis was to further elucidate the role of familial factors in the production of one component of the ERP (amplitude of P300) recorded at the brain site where it is typically maximal, the midline parietal electrode, utilizing the similarities within families. Because of the considerable interest in P300 as a possible phenotypic marker for the increased risk of developing alcohol dependence, two separate sets of families were analyzed: those with a high density of alcohol dependence and a control group of families selected for minimal presence of alcohol dependence over a three-generation span.

The path analytic TAU model of familial resemblance (Rice et al 1978) was utilized to investigate familial transmission from parent to offspring, phenotypic assortative mating, effects of common environment, and parental effects. Use of the TAU model requires the assumption that transmission of P300 amplitude may follow a multifactorial model in which both genetic and cultural factors influence the transmission from parent to offspring. The TAU model allows for the option to fit a number of submodels, including a pseudopolygenic model (a special form of polygenic inheritance in which both parents contribute equally to their offspring), which mimics genetic inheritance in intact families.

Methods and Materials

Family Data

Two samples of families each including data for three generations (grandparents, parents, and minor children) were studied. The high-risk pedigrees were ascertained through a proband pair of male alcoholics, identified through one member of the pair currently being in treatment at the time of selection (see Figure 1). The low-risk sample of families was selected for absence of alcoholism and any other DSM-III Axis I psychiatric comorbidity among the first- and second-degree relatives.

The high-risk families were part of a larger family study of alcoholism (The Cognitive and Personality Factors Family Study, CPFFS) that includes multiple extended pedigrees with multigenerational alcoholism, largely uncontaminated by other psychopathology (all first-degree relatives were required to be free of DSM-III Axis I disorders). DSM-III was the prevailing diagnostic system when the study was initiated. These high-risk families were ascertained through a proband set comprised of a pair of alcoholic brothers. On average, 2.9 first-degree relatives of the proband were alcoholic. The presence of alcoholism or other psychopathology was determined for these brothers and their first-degree relatives through face-to-face interviews (Di-

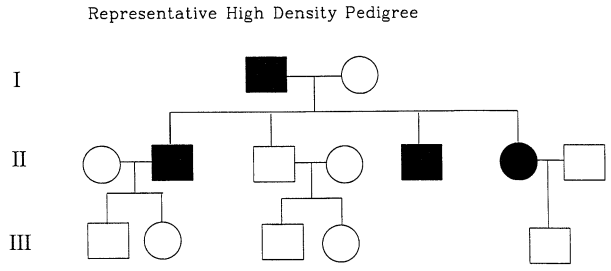

Figure 1. A high-density pedigree structure depicting the three generations (I, II, and III) used in analyses. A blackened circle or square indicates an affected individual. Low-risk families had the same three-generation structure but did not contain affected individuals.

agnostic Interview Schedule, DIS), allowing for DSM-III and Feighner Criteria (Feighner et al 1972) to be applied. The DIS was followed by a second unstructured interview conducted by a professional clinician (MA, PhD, or MD). An independent "best estimate" consensus diagnosis between the interviewer and the second clinician was then determined.

The low-risk families, who were also part of the larger study, included multiple members of pedigrees selected for absence of psychopathology from among volunteers answering advertisements for subjects to participate in a study of personality and cognition (no criteria for acceptance were advertised). Control probands, along with first-degree relatives, were similarly evaluated with the DIS and were free of all Axis I psychiatric disorders, including alcoholism. Furthermore, second-degree relatives were assessed by family history (a minimum of two reports).

ERP characteristics, including P300, were evaluated in two independent samples of families: a sample of 41 control families, and a sample of 38 high-risk families ascertained through a pair of male alcoholic probands. Personality assessment was available for all adult subjects utilized in the analysis. Data analysis was based on a total of 291 high-risk and 245 low-risk individuals in three generations (parents, siblings, spouses marrying into the family, and minor children), as given in Table 1.

Control of Contaminating Variables

All subjects were asked to refrain from using alcohol or drugs for 48 hours prior to testing. Because 113 of the persons met criteria for alcohol dependence, it was possible that many would not be able to meet our request. Therefore, the status of the drinking between the time the appointment was made and the time the test occurred was carefully assessed through the use of a clinician-administered preprotocol interview. Urine screens for known

Table 1. Demographics of the Low- and High-Risk Families Utilized in the TAU Model Analysis

Family type	N[a] Total[b]	N[a] Tested[c]	Mean age (SD)	% female	% affected
Low risk					
Mother (Gen I)	41	36	63.61 (6.0)	100	0
Father (Gen I)	41	30	65.87 (6.8)	0	0
Sibs (Gen II)	115	115	36.46 (7.1)	26.1	0
Married-in spouses (Gen II)	30	13	38.38 (4.6)	69.2	0
Offspring (Gen III)	51	51	9.94 (2.0)	45.1	0
Total		245			
High risk					
Mother (Gen I)	38	32	60.03 (6.1)	100	18.8
Father (Gen I)	38	23	62.17 (6.2)	0	47.8
Sibs (Gen II)	149	149	33.93 (7.3)	20.8	64.4
Married-in spouses (Gen II)	43	22	36.50 (3.6)	86.4	18.2
Offspring (Gen III)	65	65	9.86 (2.1)	47.7	0.0
Total		291			

Gen, generation.
[a]All subjects were Caucasian.
[b]Number of people entered into the path analysis.
[c]ERP data for some generation I and II individuals were unavailable.

Table 2. Drinking Characteristics by Generation and Gender for High-Risk Alcoholic Individuals Compared with Controls

		# days since last drink		# drinks in past 7 days[a]
Family type	*n*	Mean (SE)	Median	Mean (SE)
High risk				
Mother (Gen I)	6	578 (485)	40	3.0 (2.6)
Father (Gen I)	11	192 (154)	5	15.8 (7.9)
Male sibs (Gen II)	89	184 (82)	5	12.3 (2.1)
Female sibs (Gen II)	7	8 (3)	4	8.7 (4.7)
Low risk				
Mother (Gen I)	36			1.4 (0.8)
Father (Gen I)	30			2.5 (0.4)
Male sibs (Gen II)	85			4.6 (0.8)
Female sibs (Gen II)	30			1.4 (0.6)

[a]Drinks in past 7 days include beer, wine, and liquor.

street drugs were also performed. Although some of the alcoholic participants relapsed and could not meet the 48 hour request, most did. None had been inebriated within 24 hours of testing, and none had significant breath alcohol levels at the time of testing. As may be seen in Table 2, for male alcoholics, the median number of days since the last drink was 5 days, with alcoholic women having a median of 40 days. To assess patterns of longer term use of alcohol, blood samples were obtained from all adults to determine levels of liver enzymes (aspartate transaminase, alanine transaminase, and gamma-glutamyl-transpeptidase) known to be elevated with drinking to verify self-report data concerning recent chronic substance use. This also enabled us to exclude cases where hepatic encephalopathy was present. To insure that drug or alcohol use did not contaminate recordings obtained for the minor children included in the analysis, it should be noted that urine drug screens had been completed for 98% of these subjects.

Lifetime drinking histories were obtained for all adult subjects utilizing the format first described by Skinner (1982). Additionally, a detailed history of beer, wine, and liquor consumption for multiple time frames including 7 and 30 days was obtained for all adult subjects. Children and adolescents were evaluated for quantity, frequency, and recency of alcohol and drug use using information obtained from the Schedule for Affective Disorders and Schizophrenia–children's version interview, which they all received supplemented by a self-report instrument (Alcohol Involvement Scale). Further detail concerning evaluation of the minor children (generation III) may be seen in Hill and Hruska (1992) and Hill and Muka (1996).

All ERP recordings were conducted in the AM. All subjects were asked to eat a normal breakfast but not to consume any caffeine. Although some subjects were smokers, and among the smokers some had smoked that morning, this was noted; however, subjects were not asked to refrain from smoking, because this might have created great discomfort for some subjects, reducing compliance in finishing the tests or possibly altering the behavioral/electrophysiological response.

Electrophysiological Recordings

ERPs were recorded in all subjects using Ag/AgCl electrodes placed over the midline frontal, vertex, parietal, and occipital (Fz, Cz, Pz, Oz) locations, and left and right parietal (P3, P4) locations, referred to linked ears, with forehead ground. Ocular artifacts were monitored from an electrode placed beneath the left eye, and referred to link ears. Electrophysiological data were amplified by 20K (10K for the eye channel) using a Grass Model 12 Neurodata system, set to a band-pass of 0.01–30 Hz. The on-line rolloff is 12 dB/octave for the low filter and 6 dB/octave for the high filter. A Digital Equipment Corporation PDP-11/23 lab computer sampled each trial for a 1200 msec epoch, at 8 msec intervals with 12 bits of analog-to-digital conversion, beginning with a 200 msec prestimulus baseline. The subject's response, reaction time, and correctness of the response were encoded directly into the on-line file. Eye artifacts (blinks or eye movements) greater than 75 μV were identified visually on-line or detected automatically during off-line analysis.

The P300 component was identified off-line using a peak detection program, which searched for maximum positivity at Pz in an initial window beginning at 256 msec (or the peak of N250, if later), and extending to 416 msec. Augmented by the hard-copy plots of all ERP data, peak identification was verified visually by at least two experimenters, who could extend the search window. Experimenters were blind to the affectation status of the subject. Latency and peak-to-baseline amplitudes were automatically stored in ASCII files. The present results were limited to analyzing the P300 component at the Pz location.

Event-Related Potential Procedure

All subjects performed an auditory choice reaction time (RT) task, during which ERPs were recorded. ERPs were elicited with high (1500 Hz) and low (800 Hz) frequency tones presented in a modified version of the typical oddball paradigm. The stimuli were randomly generated by tone generator and presented every

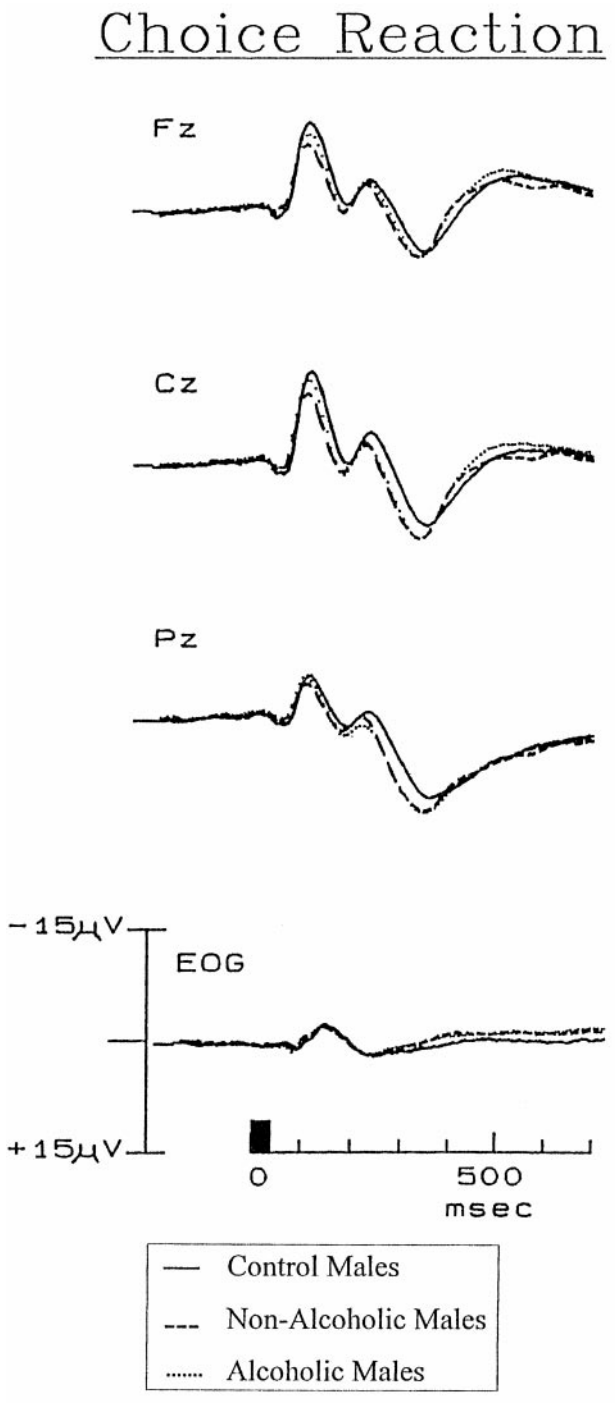

Figure 2. Grand averaged electroencephalographic waveforms at midline scalp electrode sites. Onset of the 40-msec auditory stimuli is indicated by the blackened box at time 0. Data are presented by risk groups for male subjects for the infrequent (.33) condition. Nonalcoholics are from high-risk families. EOG, electro-oculogram.

3 sec. The tones were 40 msec in duration with a 2 msec rise and fall time, at an intensity of 70 dBA. In the RT task, subjects were asked to press one button (e.g., "button on your left") when they heard a high tone and the other (e.g., "button on your right") when they heard a low tone. Subjects were randomized for conditions (right or left first), and each subject alternated on each of the required two successive blocks of 80 trials. The only restriction was that two high tones could not be presented in a row. The overall probability of a predictable low tone was .25 (low tone following a high tone), and therefore 75% of the tones (high or low tone) are unpredictable. Because we have demonstrated that P300 amplitude is dependent on the conditional probability of two tones occurring in succession, the infrequent high tones have a conditional probability of .33 (.25/.75). The .33 condition was chosen for these analyses, as this is the probability condition producing the maximal P300 response (Steinhauer and Hill 1993; Hill et al 1995a). ERP waveforms collected as part of this study are depicted in Figure 2.

Personality Assessment

All adult subjects (spouses, siblings, and their parents) were administered the Multidimensional Personality Questionnaire (MPQ) developed by Tellegen (1985). This scale was factor analytically derived and consisted of 11 primary personality dimensions (Well-Being, Social Potency, Achievement, Social Closeness, Stress Reaction, Alienation, Aggression, Control, Harm Avoidance, Traditionalism, and Absorption). High scores on Stress Reaction reflect nervous and unpredictable, changing moods. Social Closeness scores reflect the individual's need for interpersonal ties. These individuals need not be socially extroverted but rather prefer to talk with someone about their problems. The Alienation scale measures the degree to which a person feels victimized by others or "bad luck." Those scoring high on Absorption are easily captured by engaging sights and sounds. The MPQ also measures three higher order traits (Positive Emotionality, Negative Emotionality, and Constraint), which are a composite of some of the primary scales. Positive Emotionality is most similar to Eysenck's Extraversion (Eysenck and Eysenck 1975), and Negative Emotionality is most similar to Eysenck's Neuroticism dimension. Constraint is similar to Eysenck's Psychoticism dimension. Analyses were conducted with the higher order scales and with five selected primary scales.

Path Analytic TAU Models to Assess P300 in Three Generation Pedigrees

The TAU model (Rice et al 1978) was chosen to analyze the family data due to the structural characteristics of the families obtained. (LISREL programs are not appropriate for the family structure used.) In the TAU model, it is assumed that a continuous phenotype, P, may partition as $P = T + E$, where T denotes genetic and cultural factors that are transmissible from parent to offspring, and E denotes all other effects, with T and E linearly uncorrelated.

Family resemblance is determined by the path equations given in terms of standardized variables as indicated in Figure 3:

$$P = tT + eE$$

$$T_O = \tau T_F + \tau T_M + r_1 R_1$$

where *M*, *F*, and *O* denote mother, father, and offspring, respectively, and where the residual R_1 is assumed uncorrelated with *E*. The proportion of total phenotypic variance due to transmissible and nontransmissible factors is t^2 and e^2, respectively. The path coefficient, τ, measures the contribution of a parent's *T* to his offspring. In the case of polygenic inheritance, τ would be .5, and R_1 would be the segregation from midparent genotype.

Under the assumption of direct phenotypic assortative mating (mating based on observable characteristics), we can obtain the following regression equation:

$$P_F = mP_M + r_2R_2$$

where $\mathrm{COV}(R_2, P_M) = 0$, and *m* is the correlation between the phenotype of mates. It should be noted that while the arrow in the path diagram is unidirectional, this is not meant to imply that selection is only in one direction. Rather this is a convenient way to characterize the assumptions about mates with respect to components of *m* (Rice et al 1980). The correlation *c* estimates the contribution of nontransmissible environments (*E*) of full siblings. Therefore, for any pair of relatives reared in intact homes, the correlation between the relatives can be expressed in terms of the above four parameters, τ, t^2, *m*, and *c*.

Multivariate Assortment Relationships between ERP and Personality in Spouses

To adequately fit the data obtained for these families, it was necessary to further investigate the source of the unexpectedly substantial P300 correlations in mates. As a result, a conditional path method (Van Eerdewegh 1982; Vogler 1985; Carey 1986; Phillips et al 1988; Fulker 1988; Neale and McArdle 1990), implemented by the Mx program (Neale 1995), was utilized to test the multivariate phenotypic assortment relationships among P300 amplitude and selected personality traits. The Mx program yields a χ^2 goodness-of-fit statistic, which assesses the overall goodness of fit to a selected model. The agreement in the observed and the predicted variances and covariances is evaluated with a χ^2 statistic. Large values of χ^2 indicate a poor fit to the model, while a small χ^2 indicates the data are consistent with a given model.

The expected covariance matrix for spouses (Σ) is of the form

$$\Sigma = \begin{bmatrix} R_H & R_H D' R_W \\ R_W D R_H & R_W \end{bmatrix}$$

where R_W is the phenotypic covariance matrix for wives, R_H is the phenotypic covariance matrix for husbands, and D' is the matrix of conditional paths, with rows and columns corresponding to husband and wife phenotypes, respectively. Thus, the matrix *D* is computed as $D = {R_W}^{-1} M {R_H}^{-1}$. A conditional path between mate phenotypes in *D* is represented as a coefficient that measures the degree to which mates assort directly on phenotypes of interest. The parameters in the *D* matrix for P300 amplitude and the specific personality traits tested were obtained for both husbands and wives using the Mx program (Neale 1995). Homogamy is defined by the presence of nonzero correlations between husbands and wives for a particular trait.

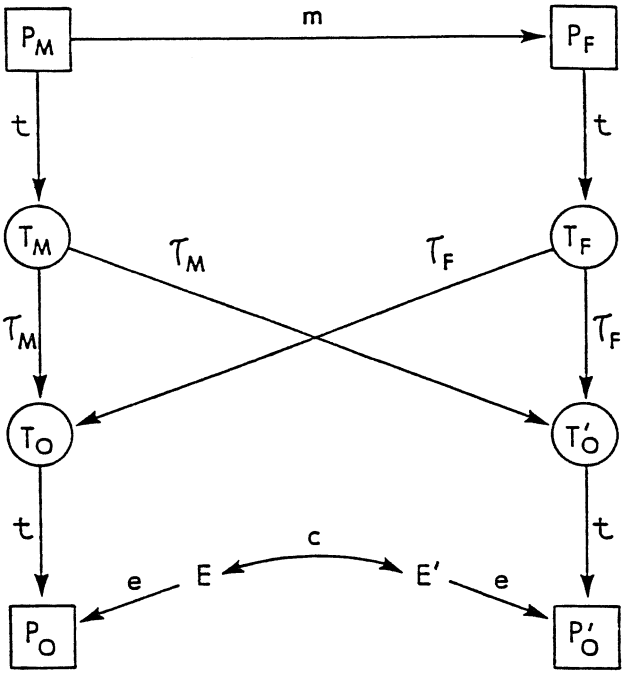

Figure 3. Path diagram depicting phenotypic resemblance between full siblings (P'_o, P_o) for the TAU model. Observed quantities are in boxes, and latent variables are in circles.

The first diagonal element of *D*, therefore, represents direct homogamy for P300 amplitude; by fixing this parameter to zero, the statistical significance of the effect of the other variable, a personality trait, could be estimated.

Results

Several publications from this data set have documented that reduction of P300 amplitude occurs in high-risk children (Hill and Steinhauer 1993a; Steinhauer and Hill 1993), though no differences were found between 98 adult male alcoholics, 39 nonalcoholic high-risk males, and 80 gender- and age-matched controls (Hill et al 1995b). ERP characteristics from these adult individuals may be seen in Figure 2. These and other negative results of studies assessing auditory P300 in adult high-risk relatives (Steinhauer et al 1987) or even adult alcoholics (Lille et al 1987; Hermanutz et al 1981) suggest that P300 may be a risk marker for later development of alcohol problems only when assessed in childhood. However, the important contribution that reduction of P300 in high-risk children appears to confer with respect to risk for later development of alcohol dependence suggests the importance of determining if patterns of transmission of this component differ within families varying on risk status (high and low risk).

The TAU model provides the opportunity for evaluating a large number of kinship correlations in terms of a few

parameters, i.e., variance of polygenic and cultural inheritance (t^2), assortative mating (m), a measure of the relative contribution to the offspring's phenotype made by each parent (τ), and a correlation between the nontransmissible environments of full siblings (c). Also, the model is well suited to family data where the unique contribution of genetic and environmental factors cannot be directly known without the benefit of an adoption design. However, there are limitations, which have been outlined by Rice et al (1980), including the fact that a pure cultural mechanism can mimic polygenic inheritance. Nevertheless, in the absence of adoption data, the model provides an estimate of familial similarity that can be instructional.

The TAU model (version 1.2 from the Genlib program) was applied to the P300 amplitude data elicited from the auditory RT task and recorded as a continuous trait, for 38 high-risk families and 41 low-risk families, respectively. Analyses were conducted separately by risk group. Correlations were first obtained utilizing the computer program FCOR (Galle et al 1991) from the SAGE software package (Statistical Analysis for Genetic Epidemiology, S.A.G.E. 1994). All P300 amplitude scores were linearly corrected for age, as P300 amplitude is age dependent. Additionally, correlations performed for the high-risk families were adjusted for affection status by setting the means dependent upon affection status. Possible differences in gender were assessed utilizing analyses within sibling pairs for each risk group type. No significant differences were seen between male and female members of generation II for the high-risk group, though differences were seen in the low-risk group that did reach significance. When the same tests were applied to the generation III subjects, no differences between boys and girls were seen. Therefore, since gender did not appear to alter the P300 amplitude significantly in most cases, analyses were not further corrected for gender.

The observed kinship correlations for P300 may be seen in Tables 3 and 4. Substantial correlations are seen for low-risk parent and child pairs (.37) as well as between siblings (.33). However, it should be noted that parent–child correlations and sibling correlations are lower in high-risk families. An unexpected finding was the existence of correlations in P300 amplitude for unrelated mates from both high- and low-risk families.

Correlations between family members were examined and may be seen in Table 5. It should be noted that the parent–son correlations in low-risk families are very similar, irrespective of whether the parent is the mother or the father. This remains true for the parent–daughter correlations as well. Similar correlations were also noted for sister–brother pairs and brother–brother pairs. Based on a smaller sample, the sister–sister correlations are much lower. The correlations in high-risk pairs differed substantially from the low-risk pairs, except for the father–son, father–daughter, and brother–brother pairs. However, mother–son correlations appeared higher than mother–daughter correlations, and father–son correlations were higher than father–daughter ones. Tests of the difference between correlations revealed no significant differences, however.

Table 3. Summary of Kinship Correlations for P300 Amplitude for the High-Risk Families Utilized in the Testing of Models

Kinship	Observed (n^a)	Expected[b]
Mates[c]	.408 (40)	.404
Parent–offspring[d]	.218 (320)	.215
Grandparent–child	.031 (103)	.100
Sibling–sibling[e]	.235 (268)	.237
Uncle–nephew	.133 (226)	.073
First cousins	−.136 (67)	.032

All data were adjusted for affection status and age before correlations were calculated.
[a]Number of pairs.
[b]Predicted correlations at the best fit for the TAU model.
[c]Correlations based on pairs from generation I and from generation II spouses.
[d]Parent–offspring pairs include both generation I–II and generation II–III.
[e]Siblings include generation II and generation III subjects.

The predicted correlations at the point of best fit from the TAU model are given in the second columns of Tables 3 and 4 for the high- and low-risk groups, respectively. The parameter estimates obtained by fitting the TAU model to the observed correlations (from Tables 3 and 4) for the high- and low-risk families are displayed in Table 6.

High-Risk Families

Table 6 displays the four estimated parameters (e^2 is derived from $1 - t^2 - c^2$) of the general TAU model which achieved a good fit ($\chi_2{}^2 = 3.142$, $.1 < p < .25$) for the high-risk families. To test whether the observed data gave evidence for polygenic inheritance (pseudopolygenic model), τ was fixed to .5, and the other variables were free to vary. In this situation, it is assumed that the mother and father equally contribute both genetic and cultural factors to the child. The parameters obtained under the pseu-

Table 4. Summary of Kinship Correlations of P300 Amplitude for the Low-Risk Families Utilized in the Testing of Models

Kinship	Observed (n)	Expected
Mates	.359 (39)	.363
Parent–offspring	.374 (262)	.351
Grandparent–child	.110 (77)	.135
Sibling–sibling	.328 (164)	.315
Uncle–nephew	.009 (142)	.087
First cousins	−.121 (39)	.030

All data were adjusted for age before correlations were calculated.

Table 5. Kinship Correlations of P300 Amplitude Illustrating Similarity of Correlations within and across Gender for the High- and Low-Risk Families

	Low risk		High risk[a]		
Kinship	*n*	Observed	*n*	Observed adjusted	Observed unadjusted
Mother–son	96	.447	125	.293	.275
Father–son	85	.426	102	.443	.365
Mother–daughter	40	.320	50	.035	.134
Father–daughter	41	.272	43	.281	.169
Sister–brother	77	.364	115	.105	.133
Brother–brother	62	.432	142	.330	.318
Sister–sister	25	−.020	11	.105	.055
Grandparent–child	77	.196	103	.073	.070

[a]Correlations for high-risk individuals are presented adjusted for affection status and unadjusted. All correlations were computed with the S.A.G.E. program, FCOR.

dopolygenic model (fixing $\tau = .5$) are also displayed in Table 6. Using the likelihood ratio test to compare the pseudopolygenic model ($\tau = .5$) to the general multifactorial model revealed a result ($\chi_1^2 = 0.212$, $p > .5$) that does not clearly indicate a better fit for one model over the other. The variance of the transmissible factor, t^2, for the high-risk families is 29% under the assumption of the pseudopolygenic model and 38% under a multifactorial model; however, the value for the pseudopolygenic model (.291) is significantly different from 0.

Low-Risk Families

The pseudopolygenic model (τ fixed at .5) was tested and compared to the τ of .292 (see Table 6) for members of families belonging to the low-risk group. This model was rejected ($\chi_1^2 = 4.56$, $.025 < p < .05$). Based on the observed variation in P300 among low-risk family members, under a general multifactorial model, the estimate of t^2 obtained is 88%. This value of t^2 was significantly different from 0.

Comparison of High- and Low-Risk Families

The total variance of familial transmission, t^2, was compared for high- and low-risk families and found to be significantly different ($t = 7.57$, df = 2, $p < .02$). Transmissible factors between parents and children were found to be greater for high-risk than for low-risk families ($\tau = .40$, SE = .16 for high-risk and $\tau = .29$, SE = .03 for low-risk families). Testing these values revealed a significant difference in parental transmission ($t = 7.7$, df = 2, $p < .02$). This finding is intriguing, because it suggests that parental effects are more important in high- than low-risk families. If P300 is a marker for later development of alcohol dependence, as numerous studies now suggest, then factors related to increased transmission of P300 characteristics through parent–child effects may be

Table 6. Summary of Parameter Estimates (SE) and χ^2 Goodness-of-Fit Statistics for Hypotheses Testing Using Kinship Correlations

	Low-risk families		High-risk families	
	General model	Pseudopolygenic model	General model	Pseudopolygenic model
τ	**.292 (.027)**	.5	.404 (.156)	**.5 (fixed)**
m	**.363 (.102)**	.352 (.106)	.404 (.098)	**.403 (.098)**
t^2	**.884 (.058)**	.465 (.065)	.380 (.183)	**.291 (.052)**
c	**1.000[a] (.00)**	.091 (.112)	.152 (.127)	**.104 (.070)**
e^{2b}	**.116**	.535	.596	**.709**
	$\chi_2^2 = 1.948$	$\chi_3^2 = 6.540$	$\chi_2^2 = 3.142$	**$\chi_3^2 = 3.354$**
	$.30 < p < .50$	$.05 < p < .10$	$.20 < p < .30$	**$.30 < p < .50$**

Accepted model is indicated in bold. τ, the extent to which transmissible factors of a parent influence the transmissible factors in the offspring; *m*, the correlation between mates for the trait; t^2, the proportion of the total phenotypic variance that is transmissible (both cultural and genetic) from all sources, including but not limited to parents; *c*, common or shared environment represented by the correlation between the nontransmissible environments of siblings; e^2, the total variance due to nontransmissible factors.

[a]Converged to the boundary.

[b]Derivative parameter.

important. van Beijsterveldt (1996) has interpreted findings obtained for adolescent twins as indicating that up to one half of the variance in P300 amplitude may be due to variables not manipulated in one's experiment, such as arousal state during the session, task motivation and attention, or error variance. Thus, parents may contribute a cognitive style (e.g., tendency for arousal, low or high motivation to perform) to their offspring. Whether this style is transmitted by cultural or genetic means cannot be determined, however.

Phenotypic Correlations in Mates for P300

Possible explanations for the substantial spousal correlations in P300 amplitude seen for both high- and low-risk families with the TAU model ($m = .41$, SE = .10 for the high-risk and $m = .36$, SE = .10 for the low-risk) were explored. The positive correlations seen between mates could be due to direct phenotypic assortment, as first described by Cloninger et al (1979) based on the formula of Fisher (1918). However, direct assortment may only be apparent and secondary to the actual causes of the phenotypic correlation observed. The actual source of the correlation may be genetic factors, cultural factors transmitted between generations, or environmental experiences relevant to the development of phenotypes that are not transmitted between generations.

Assuming the phenotypic correlations resulted from mate selection, it was of interest to determine if a primary source of variation having greater plausibility than direct assortment for P300 could be found. Accordingly, selected personality variants were explored as a possible source of the positive mate correlations.

Hypothesis testing about direct homogamy for P300 amplitude was performed on the conditional path D matrix, controlling for specific personality factors for the high- and low-risk families, respectively. The traits selected were Social Closeness, Stress Reaction, Alienation, Aggression, and Absorption. (Due to the limited matrix dimensions available in the Mx program, a maximum of five personality traits could be considered.) Under the multivariate assortment method, the five traits were tested together. These five primary scores were chosen based on results obtained for within-family correlations obtained in a previous study of high- and low-risk families (Hill et al 1990), in which mates showed significant correlations in personality (Social Closeness was correlated within low-risk mates and Alienation was correlated in high-risk mates). Also, sibling correlations obtained in the earlier study suggested the potential importance of Aggression, Stress Reaction, and Absorption (Hill et al 1990). Separate analyses were also conducted using the three higher order traits (Positive Emotionality, Negative Emotionality, and Constraint).

High-Risk Families

Forty spouse pairs were tested for P300 amplitude and the three higher order personality traits. A 4 by 4 dimensional matrix, D, with rows and columns corresponding to the husband's and wife's phenotypes (P300 amplitude, Positive Emotionality, Negative Emotionality, and Constraint), was constructed. The first test on this D matrix was for symmetry. A symmetry test applied to this matrix yielded a nonsignificant result ($\chi_6^2 = 6.19$, $p > .25$), indicating that gender was not a factor in any assortment detected. Accordingly, this model was adopted for subsequent comparisons with reduced models. Thus, the correlation of the wife's P300 amplitude and the husband's personality traits did not significantly differ from the wife's personality traits and the husband's P300.

Next, direct homogamy for P300 amplitude was tested (diagonal element of matrix D is set to zero). Although the goodness of fit was acceptable ($\chi_7^2 = 10.89$, $p > .1$), the likelihood ratio chi-square was significant ($\chi_1^2 = 4.7$, $p < .05$) when compared with the previous model. Accordingly, homogamy between the personality factors and P300 was rejected. Thus, the spousal similarity in P300 was not due to direct assortment for the three higher order MPQ personality traits tested in the high-risk families.

Low-Risk Families

Data were available for 37 spouse pairs from the low-risk families. As was the case for high-risk mates, P300 was correlated within spouses, independent of the higher order personality traits studied. Possible effects of gender upon any homogamy detected were evaluated in the low-risk families and found to have no effect. [The symmetry model for the D matrix was accepted (goodness of fit, $\chi_6^2 = 1.89$, $p > .75$).] Direct homogamy was not found (goodness of fit, $\chi_7^2 = 15.08$, $p < .05$). In addition, this homogamy model when compared to the symmetry model was significant ($\chi_1^2 = 13.19$, $p < .005$), further indicating that the homogamy model could be rejected. As was found for the high-risk spouses, low-risk ones appear to also demonstrate direct homogamy for P300, which is independent of the personality traits tapped by the higher-order scales utilized in the analysis.

Effect of Primary Scales from the MPQ upon Mate Correlations

The conditional path method utilizing higher order factors did not reveal a source for the P300 correlations observed in spouses for either high- or low-risk families. Therefore, selected primary personality traits (five scales of the MPQ) were subsequently examined, using the same conditional path methods. Direct homogamy for P300 ampli-

tude (first diagonal element of matrix D) was again significantly different from zero (the difference in likelihood, $\chi_1^2 = 3.90$, $p < .05$) for high-risk families as well as for low-risk families ($\chi_1^2 = 13.19$, $p < .001$). These results indicated unexpectedly high correlations in mates (both high and low risk) that are independent of the personality traits examined in this study. Thus, we could not identify specific observable factors (e.g., personality) in spouses that could have resulted in such a high degree of similarity in a nonobservable trait, such as P300 amplitude. How an individual might select a mate resulting in a similarity on this dimension is unknown. Mate selection might have been based on a trait that resulted in P300 similarity (e.g., attention, motivation, or personality variants not tested); however, there is evidence that the personality of spouses becomes more alike over time (Price and Vandenberg 1980).

In searching for explanations other than direct or indirect assortment, shared and nonshared environmental factors must be considered. It has been demonstrated by van Beijsterveldt et al (1996), utilizing adolescent monozygotic and dizygotic twin pairs, that approximately 50% of the variance in P300 is due to environmental factors. What are the factors that could have produced greater similarity in mates than in random pairs of individuals? With respect to shared environment, these spouses can be expected to have acquired similar habits with respect to meal time, bedtime, number of hours of sleep, and living in either a quiet or noisy home or neighborhood. All of these factors may be influential. For example, Geisler and Polich (1992) have shown that fasting state influences the P300 component. Similarly, sleep deprivation prior to the ERP recording also has been shown to affect both P300 amplitude and latency (Morris et al 1992). Thus, numerous experiences shared by persons from the same household could contribute to similarities in physiological processes including event-related potentials. However, factors other than common environment also appear to play a significant role based on the substantial correlations seen in adult siblings (generation II), most of whom lived in separate households.

Discussion

Rice et al (1978) first developed models for testing multifactorial inheritance of complex traits that allow for cultural transmission and assortative mating. In that seminal report, methods are described for comparing submodels of a unitary multifactorial model: a polygenic one in which all transmissible factors are due to the effects of additive genes, a cultural model in which transmission is due entirely to the effects of culture, and a pseudopolygenic one in which transmission from parent to child is 1/2, a condition that mimics polygenic inheritance. Although the TAU model that was further elaborated (Reich et al 1980) did not partition the transmissible variance into that which is genetic and that which is cultural, it did allow for hypothesis testing and for approximate estimation of the combined effects of both.

Other path analytic models have been elaborated more recently (Neale and Cardon 1992; Neale 1995). However, these models, like the BETA model (Cloninger et al 1979), which allows for partitioning t^2 into additive genetic inheritance and cultural inheritance, require an estimate of resemblance in twins (monozygotic compared to dizygotic twins, ideally reared apart), or adoption data to evaluate possible environmental effects upon P300 resemblance. Thus, because twin and adoption data were not collected within the present study design, the analysis was restricted to conclusions that could be derived from application of the multifactorial (TAU) model as originally elaborated by Rice et al (1978).

The goal of the present report was to evaluate within-family transmission as a function of risk status inasmuch as P300 amplitude had been implicated as a risk marker for later development of alcoholism. The lesser degree of variance due to overall familial transmission observed for the high-risk families (29% versus 88% for the low-risk families) may have been due to subtle differences in the effects of chronic alcohol abuse in some, but not all, family members. Although the analysis controlled for affection status among members of the high-risk families, varying degrees of cognitive impairment due to alcohol use might have increased error variance in the high-risk group, thus reducing the strength of the correlation.

Of particular interest was the finding for parent–offspring transmission, in which high-risk families exhibited a greater τ than did low-risk families (40% versus 29%). This indicates that the transmissible factor (P300) in high-risk parents is transmitted to offspring more than is the case between low-risk parents and their offspring. The extensive literature suggesting the importance of P300 amplitude as a marker for alcohol dependence when measured in offspring of alcoholic parents, particularly when assessed in childhood (Begleiter et al 1984; Berman et al 1993; Hill and Steinhauer 1993a; Hill et al 1995a, 1995c), suggests the particular relevance of P300 amplitude as one pathway in the etiology of alcohol dependence.

As originally noted by Reich et al (1980), when tau values approach .5, one has better evidence for polygenic inheritance; however, unfortunately a value close to .5 can also be the result of cultural transmission, which can mimic polygenic inheritance. Thus, because a tau of .404 is closer to .50 than is .292, it appears that the high-risk families show a greater likelihood of transmission from parent to offspring. Under the assumption of a polygenic

explanation, the possibility exists that assortative mating for alcoholism or some observable trait like personality variation might play a role. For example, if a yet unidentified genetically mediated trait, e.g., a transmissible personality trait, were found to be highly correlated with P300 amplitude, and mates choose one another on the basis of this trait, parent/offspring transmission could be increased by genetic means. Also, environmental effects provided by an alcohol-abusing parent may be more transmissible to offspring than is the case in nonabusing parents. This would be particularly so if the environmental effect (e.g., less attentional focusing) is highly correlated with P300 production in an information-processing task.

Of interest was the striking difference observed in the covariances of the siblings environments between the high-risk and low-risk families (.104 for high-risk and 1.00 for low-risk families). This suggests that the nontransmissible factors in the common environment of siblings in high-risk families may be more unique for each sibling than it is in low-risk families. This is consistent with early observations by Wolin and colleagues (Wolin and Bennett 1984; Wolin et al 1980) that the family environment of alcoholics is quite variable. These investigators were able to identify families in which alcohol dependence was transmitted at higher rates than those in which it was not. Interestingly, the families who were able to maintain their family rituals in spite of the disruptive effects of living with an alcoholic parent were protected from transmitting alcohol dependence to the next generation. Possibly this effect varies from sibling to sibling, some viewing the disruption of family rituals of holidays and mealtime as greater or lesser depending on their age, gender, and temperament.

A separate issue to consider is the overall transmission of P300 represented by t^2. Here, low-risk families appear to show greater transmission. Although this would appear to be at odds with the finding of greater transmission from parent to offspring in high-risk families, in fact it is not. The explained variance provided by t^2 takes into account all sources of variance that are transmissible (i.e., both cultural and genetic from all sources including, but not limited to parents). As previously noted, the variance due to common environment effects in siblings was found to be quite different between high- and low-risk families. This suggests that the impact of alcoholism in the family decreases the common family environment of siblings in such a family. Accordingly, to the extent that t^2 includes variance due to common environment, one can see that low-risk families might be expected to exhibit greater similarity in P300 amplitude.

Of course other sources of variation between siblings may contribute to the present findings, including those due to gender—gender of the parent and of the offspring. In general, the parent-to-son correlations in P300 were higher than the parent-to-daughter correlations in the low-risk families (about 1.5 times higher for male offspring than female offspring); however, in high-risk families this relationship was less clear. Mother-to-son correlations were lower than the father-to-son correlations in P300 amplitude. Also, mother-to-daughter correlations, though of the same gender, were lower than they were for father to daughter.

The present results are consistent with recent results obtained in samples of twins studied in the Netherlands (van Beijsterveldt 1996) and in the U.S. (O'Connor et al 1994). Neither of these samples were selected for the presence or absence of psychiatric problems, however. In a study of over 200 adolescent twins, van Beijsterveldt (1996) found the variance explained by genetic factors to be 42% for targets tones, when results of ERP assessments were analyzed using an additive genetic/nonshared environmental effects model. O'Connor et al (1994), studying adult twins, found P300 amplitude to be significantly heritable, with variance ranging from .41 to .60, suggesting genetic dominance is involved in the transmission. No significant heritability was seen for P300 latency.

We are unable to explain the high correlations in mates for P300 seen in both high- and low-risk families. There may be assortative mating for other observable traits in mates that may differ by the risk status of the individual. There are a number of reports documenting the similarity in personality among mates (Price and Vandenberg 1980; Mascie-Taylor and Vandenberg 1988). Similarities in arousal/stimulation seeking have also been reported in couples (Farley and Davis 1977). There are both positive and negative reports (Cahill and Polich 1992; Polich and Martin 1992) concerning the role of personality in the production of P300 amplitude. Selection by personality traits in mates might offer one explanation for the similarity observed in this study for P300 in mates. Another possibility is that a shared environment may be contributing to the increased similarity observed in spouses who live together.

Previously, we observed significant correlations in personality (Alienation) for mates from our high-risk sample (Hill et al 1990). Although the personality dimensions tapped by the MPQ did not appear to influence the kinship correlations observed with P300 amplitude in the present analysis for either family members or mates, it is possible that other personality variants, not tested in the present study, do exist that influence the amplitude of the P300 component in response to task demand. For example, novelty seeking, measured with the TPQ (Cloninger 1987a, 1987b), has been shown to be associated with a predisposition for developing substance abuse (Cloninger et al 1988). Therefore, spouses who assortatively mate for

novelty seeking may have similar ERP components, especially if P300 and novelty seeking are both markers for a predisposition to alcoholism. Still other factors may play a role. If the amplitude of P300 is in part determined by motivation and attention, one might speculate that persons who become mates may be more similar on these dimensions. Our analysis utilized a personality trait previously found to be correlated in high-risk mates (Alienation), or ones positively correlated within concordantly affected sib pairs (Aggression and Absorption), or in discordant pairs (Stress Reaction). Introduction of these traits failed to alter the results obtained for P300 in mates, so that we must conclude that the couples are assortatively mating for an observable trait, yet to be identified, that is correlated with P300 amplitude. Further work is needed to understand the mate correlations observed, as they may suggest a mechanism whereby gene pooling for traits associated with alcoholism risk might occur.

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