Eight-Year Longitudinal Follow-up of P300 and Clinical Outcome in Children from High-Risk for Alcoholism Families

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Introduction

The possibility that the P300 component of the event-related potential (ERP) may have etiological significance for alcoholism has been discussed for over a decade now (Pfefferbaum et al 1979; Hill et al 1986). A number of cross-sectional studies (Begleiter et al 1984; Hill et al 1990; Whipple et al 1991) have demonstrated decrements in the amplitude of P300 in high-risk children. Only one study followed children (4 years) to determine behavioral outcome (Berman et al 1993), although reassessment of P300 was not done. Based on a self-report questionnaire, those with the lowest P300 amplitude at baseline were more likely to be involved with substances 4 years later. Because of the high density of alcoholism in our families, we expected that a high proportion of the children whom we have been following might develop alcoholism at an early age. In fact, our sampling strategy has enabled us to study a severe form with early onset that emerges in spite of a favorable environment (Hill 1992). These children provide an opportunity to evaluate P300 as a predictor of substance abuse.

Methods

Subjects

A pilot study involving 22 children from high- and low-risk for alcoholism families was initiated in 1985. The children had been ascertained through the Cognitive and Personality Factors Family Study initiated in 1984. The pilot sample was later expanded to include 120 children who, by study design, were at either high or low-risk for developing alcoholism, and who are currently being evaluated longitudinally. The high-risk children (HR) have an average of 3.9 first- and second-degree relatives who are alcoholic and the low-risk (LR) control children are without first- or second-degree relatives with alcoholism and only minimal axis I psychiatric disorders (e.g., no recurrent depression or schizophrenia).

Because the longest follow-up available addressing the predictive power of P300 to determine substance abuse outcome is only 4 years (Berman et al 1993), it seemed reasonable to attempt to locate and assess outcome along with ERP characteristics at retest for this pilot sample of children, a sample that had the potential for an 8 year follow-up. It was possible to locate and include 20 of the initial 22 children tested for ERP characteristics at baseline in 1985, interview them for psychiatric status, and retest them in our ERP laboratory (Table 1).

ERP Procedure

At both baseline and follow-up, auditory ERPs were elicited with high (1500 Hz) and low (800 Hz) tones (40 msec duration; 3 sec interstimulus interval; 70 dBA intensity) presented in a modified oddball paradigm as previously described (Steinhauer et al 1987; Hill et al 1988, 1990; Steinhauer and Hill 1993). High-pitched tones occurred 25% of the time; subjects were told only that two high-pitched tones could not occur in a row. Thus, three conditions could be identified by their conditional sequential probability: an unpredictable rare high tone ($p = 0.33$), an unpredictable low tone ($p = 0.67$), and the predictable low tone ($p = 1.00$) that occurred after each high tone. The condition with a probability of 1.00 was the "certainty" condition due to prerecording instruction to subjects that two high-pitched tones

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could not occur in sequence. A Choice Reaction task was used to elicit the ERPs.

In the choice reaction 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 the low tone. Subjects were randomized for which came first (right or left), and each subject alternated on each of the required two successive blocks of 80 trials.

Electrophysiological Recordings

Event-related potentials were recorded using Ag/AgCl electrodes placed over the midline frontal, vertex, parietal, and occipital (Fz, Cz, Pz, Oz) locations, left and right parietal (P3, P4) locations, and referred to linked ears, with forehead ground. Data were amplified by 20K (bandpass = 0.01–30 Hz) and digitized at 8 msec intervals for 1200 msec. Trials with eye artifacts (blinks or eye movements) greater than 75 μV were rejected.

ERP Data Analysis

Artifact-free trials were averaged for each condition and electrode. Two raters, blind to group membership, identified the ERP components using an interactive computer algorithm that chose the maximal amplitude for a given component (at Pz for P300) within a predefined latency window (264–464 msec for P300).

Clinical Evaluation

At follow-up a clinician, blind to group status, administered the age-appropriate structured interview (Diagnostic Interview Schedule [adults] or K-SADS [children under 18]). A "best estimate" diagnosis was reached utilizing the consensus of two interviewers, one performing the structured interview and a second follow-up by a resident psychiatrist.

Table 1. Demographic Characteristics and Temporal Stability of P300 Amplitude for High- and Low-Risk Children (Mean and Standard Error)

	High-risk		Low-risk	
	Baseline	Follow-up	Baseline	Follow-up
Age (yrs)	10.73	18.80	9.78	17.89
	0.60	0.48	0.70	0.70
Gender M	4	4	2	2
F	7	7	7	7
Number of alcoholic relatives	4.0	4.0	0.0	0.0
P300 Amplitude (μV)[a]	13.77	10.57	18.05	17.38
	1.72	1.51	2.50	1.10

Notes. Test–retest reliability for the entire sample from baseline to follow-up: $r = 0.45$, $p < 0.05$; for low-risk, $r = 0.82$, $p < 0.01$.

[a] Session effects that evaluated baseline to follow-up *within*-group differences were not significant due to the stability of auditory P300 amplitude in this sample of predominantly young girls.

Table 2. Analysis of Variance of P300 Amplitude and Latency for Baseline and Follow-up Assessments

Effect	*F*	*df*	*p*
Amplitude			
Risk group (HR/LR)	7.55	1,18	.013
Probability	83.98	2,31[a]	<.001
Session (baseline to follow-up)	1.73	1,18	N.S.
Latency			
Risk group (HR/LR)	0.05	1,18	N.S.
Probability	11.85	2,34[a]	<.001
Session (baseline to follow-up)	22.79	1,18	<.001

Note. No significant interactions were found for either amplitude or latency.

[a] Greenhouse–Geisser-corrected degrees of freedom to adjust for repeated measures.

Results

P300

Amplitude and latency of P300 at Pz were analyzed using an analysis of variance for Group (HR and LR), Probability (0.33, 0.67, 1.00), and Session (baseline and follow-up). P300 amplitude was significant for Group and Probability (Table 2). The Group effect for P300 amplitude, which was based on 40 observations (20 at age 10 and 20 at age 18), was significant at $p = 0.013$ and indicates that children at high-risk for alcoholism have lower P300 amplitudes on the whole than do low-risk children. Differences at follow-up may be seen in Figures 1 and 2. The Session effect was not significant, indicating that across all probability conditions and risk groups the auditory P300 amplitude from time 1 to time 2 did not differ (Table 1). This does not preclude specific age and gender groups from exhibiting developmental changes. For example, we have previously noted important differences in maturation of the visual and auditory P300 by gender (Hill and Steinhauer 1993; Steinhauer and Hill 1993). We speculate that session effects due to changes associated with maturation were not seen due to the unbalanced gender composition of the sample. Girls remain relatively more stable than boys in auditory P300 amplitude from childhood through adolescence.

For latency of P300, the Group effect was not significant (Table 2). Lower event probability was associated with longer latency. The Session effect was significant due to the latency becoming shorter as the children matured.

Clinical Findings

Four of the 11 HR children had developed alcoholism by Research Diagnostic Criteria (RDC) by the time of follow-up; none of the controls met criteria for a substance abuse disorder. The exceptionally high rate of substance abuse among the HR children who are now young adults (18.8 years of age) is

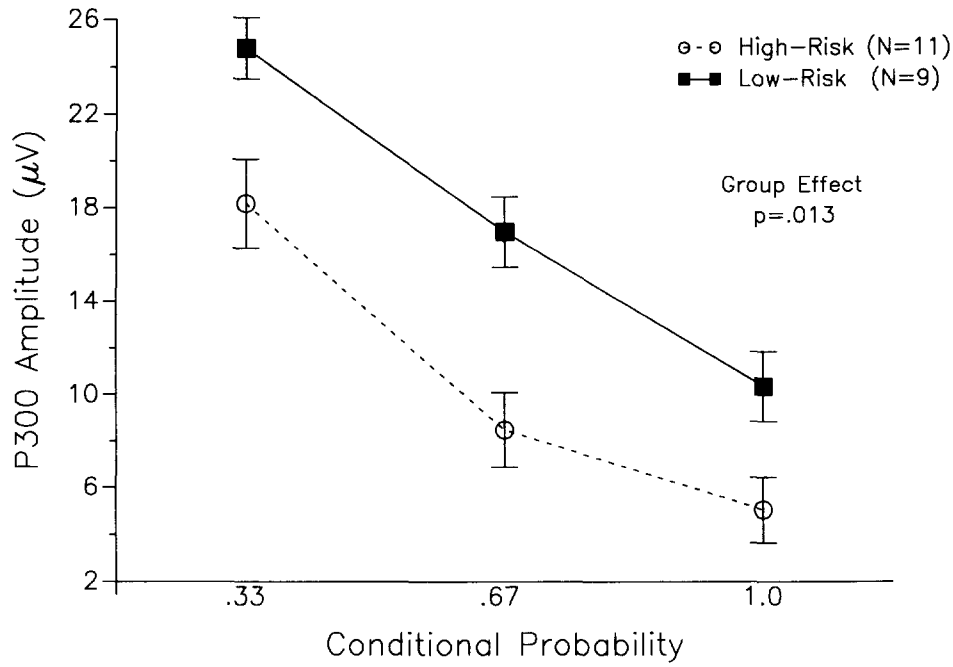

Figure 1. High- and low-risk group differences in P300 amplitude at 8 year follow-up (average age was 18.8 years) are displayed. Significant differences are found for each conditional sequential probability; an unpredictable rare high tone ($p = 0.33$), an unpredictable low tone ($p = 0.67$), and the predictable low tone or "certainty" condition (conditional probability = 1.00). Probability effects reflect expected differences in the meaningfulness of the stimuli due to the relative rarity of the event. These high-risk for alcoholism young adults continue to display reduction in amplitude, as was seen at baseline when the children averaged 10.7 years (graph represents follow-up data). Across all probability conditions and across both risk groups, there were no significant differences in P300 amplitude by session (baseline and follow-up). Expected maturational effects for this predominantly female sample were seen (either a slight reduction or no change from age 8 to 18 years).

probably due to the exceptionally high familial density of alcoholism afforded by the study design.

P300 As a Biological Marker of Clinical Status

In order to determine if the differences by group were related to clinical status, a t test was calculated using lifetime presence or absence of alcohol dependence and the amplitude of P300 in the 0.33 condition at follow-up. Of the 20 subjects studied, four met criteria for alcohol dependence (all from the HR group). Although this study involved only a small pilot sample, we find that the four individuals who developed substance abuse problems had significantly lower P300 in the infrequent probability condition ($p = 0.33$) at follow-up than did 16 children who had not ($t = 2.56$, $df = 1,18$, $p = 0.020$).

To determine if the association was specific to alcoholism and not externalizing psychopathology, the phenotype was broadened to include the presence of any externalizing disorder, including alcohol dependence. With this phenotype, a comparison was made between these six individuals (two with Conduct Disorders, four with alcohol dependence) and the remaining 14 individuals who by age 18 were either without any diagnosis or had what appeared to be a more transient internalizing disorder of childhood (e.g., separation anxiety). No significant difference was found ($t = -1.11$, $df = 1,18$, $p = 0.281$).

Discussion

P300 amplitude reduction may be a specific vulnerability marker for alcoholism risk (Hill and Steinhauer 1993; Steinhauer and Hill 1993), as one indicator of risk for schizophrenia (Zubin and Spring 1977), or perhaps serve as a nonspecific vulnerability indicator (see Friedman 1991 for review). Squires-Wheeler et al (1993) have followed high-risk for schizophrenia children from age 15 to 25, finding a relationship between P300 decrements at age 15 and poorer Global Personality Functioning at age 25.

A considerable body of evidence suggests that brain neuroelectrical activity, including event-related brain potentials, is heritable. A high degree of similarity in siblings has also been demonstrated, with correlations ranging between 0.61 and 0.82 depending on the task used to elicit the P300 (Steinhauer et al 1987). Recently, ERP data from a large family study of alcoholism has been analyzed using segregation analysis to determine possible modes of inheritance of the P300 component, with

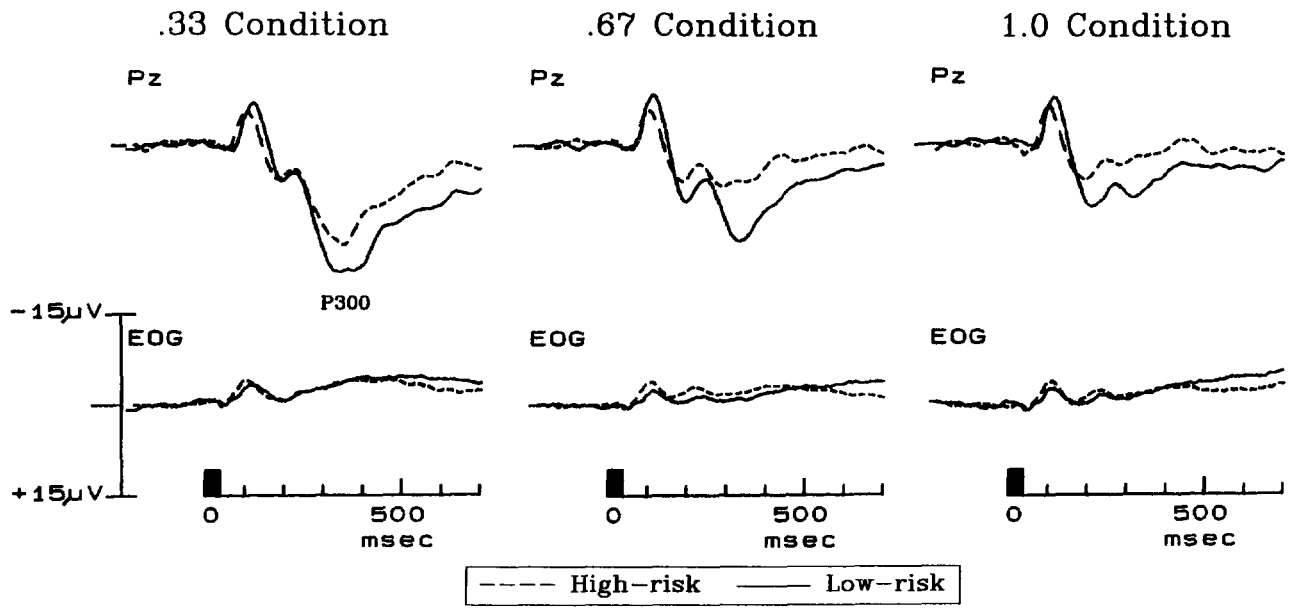

Figure 2. Grand mean auditory (Choice Reaction Task) ERPs at the parietal electrode, superimposed to illustrate differences in the waveform for the high- and low-risk groups. A modified oddball paradigm was utilized with the infrequent high tone presented randomly 25% of the time. The conditional sequential probabilities (0.33, 0.67, and 1.00) represent the unpredictable rare high tone, an unpredictable low tone, and a predictable low tone, respectively. The 1.00 condition is also known as the "certainty" condition because subjects are told before recording that two high tones cannot occur in a row; presentation of a high tone means a low tone can be predicted with certainty. Note the smaller amplitude of P300 for the high-risk group compared to the low-risk group at each conditional probability.

evidence presented for a major gene controlling the familial similarity in P300 amplitude (Aston and Hill 1990; Aston et al, submitted).

In summary, the present study is unique in having recorded P300 at two different times separated by follow-up of nearly a decade. With the demonstrated genetic mediation of the expression of P300 amplitude, it is especially interesting that P300 amplitude was significantly different between the HR and LR groups at follow-up. The fact that the HR children who had already developed alcohol dependence differed from the remainder of the sample is also intriguing. Moreover, the fact that P300 did not differ between groups designated as "any externalizing disorder" and those designated "no externalizing disorder" seems to suggest the specificity of the auditory P300 amplitude as a marker for alcoholism risk.

Therefore, the present results are particularly interesting in that they suggest that the intergenerational nature of alcoholism might be identified in particular cases through the P300 component. With a biological marker in hand, prevention efforts may be more focused on those at greatest risk, providing an opportunity to break the intergenerational cycle in families prone to develop alcoholism.

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