Developmental Delay in P300 Production in Children at High Risk for Developing Alcohol-Related Disorders

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Background: *Reduction of P300 amplitude in children and adolescents at high risk for developing alcoholism has frequently been reported. It has been hypothesized that this reduction represents a developmental delay in reaching age-appropriate levels in P300 amplitude. Using latent growth analysis of longitudinal data obtained at yearly intervals, this study seeks to define normal growth, and determine if the pattern seen in high-risk children differs from that obtained in normal low-risk controls.*

Methods: *A total of 156 children from either high or low-risk families have been assessed multiple times (two-thirds more than 4 times) using both a clinical assessment (K-SADS) and ERP evaluation performed on the same day. A total of 635 separate assessments were available for modeling.*

Results: *Quadratic growth curves revealed a slower rate of change in P300 amplitude in high-risk than low-risk males. High-risk girls showed reduced visual P300 amplitude only when the presence of a K-SADS diagnosis was considered. No differences were seen for P300 latency.*

Conclusions: *This study confirms the hypothesis that when reduction of P300 amplitude is seen in males at high risk for developing alcoholism, it is due to a developmental delay.* Biol Psychiatry 1999;46:970–981 © *1999 Society of Biological Psychiatry*

Key Words: Alcoholism, high-risk offspring, P300, developmental delay, K-SADS, childhood psychopathology

Introduction

The P300 component of the event-related potential (ERP) has been extensively studied in alcoholics and their high-risk relatives in an effort to find a biological marker of alcoholism risk. Adult alcoholics present a problem for understanding whether the P300 component is a risk marker because neuropathological changes resulting from long term use of alcohol confound the picture. Alcoholics tested in ERP paradigms usually have long drinking histories (usually over 12 years) and very short periods of abstinence when tested (usually only two weeks) (Porjesz et al 1987a). Alcoholics who have been abstinent for 3 months or more do not display reduced P300 amplitude in either the auditory or visual modality (Biggins et al 1995). Thus, the stage of acute (usually lasting days to weeks) or protracted withdrawal (months or years) experienced by the alcoholic at the time of testing is an important determinant of P300 amplitude and latency. In addition, the presence of comorbid disorders, particularly those known to affect P300 amplitude such as depression (Bruder et al 1995; Blackwood et al 1987; Yanai et al 1997) may cloud the interpretation of the results obtained. The critical question is whether P300 reduction, if seen, was present before the alcoholic individual began to drink. Thus, the P300 component of the event-related brain potential has been evaluated as a possible biological risk marker for the development of alcoholism in numerous studies involving children and adolescents (Begleiter et al 1984; Hill et al 1987) for over a decade now.

Developmental Changes in P300

The P300 is a scalp positive wave that occurs approximately 300 msec after an informative stimulus occurs (Sutton et al 1965). Because the P300 component of the ERP is an electrophysiological index of an individual's capacity to process stimulus information, both P300 amplitude and latency have been studied in samples thought to vary on some neurocognitive, behavioral, or maturational dimension. Substantial differences in the event-related potentials of adults and children have been reported (Courchesne 1977; Kurtzburg et al 1984). Although the P300 component has been studied widely with respect to both normal (Polich et al 1990; Courchesne 1978) and cognitively challenged children, for example, Downs Syndrome children (Courchesne and Yeung-Courchesne 1988), few studies have specifically varied experimental groups by age to assess developmental changes during childhood and adolescence. As may be seen in Table 1, less than 200 children have been studied in designs of this

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Table 1. Summary of Findings for Previous Studies Assessing Age Effects in Children and Adolescents

Study	Age range (years)	Total *n*	Modality	Findings
Ladish and Polich 1989	5–9, 10–14, 15–19	36	Auditory	Increases with age
Polich et al 1990	4–6, 7–9, 10–12, 13–15, 16–18, 19–20	50	Auditory	Increases with age
Courchesne and Yeung-Courchesne 1988	5, 7, 12, 16, and 28	25	Auditory	Increases with age
Courchesne 1977	6–8, 23–35	20	Visual	Decreases with age
Courchesne 1978	6–8, 10–13, 14–17	48	Visual	Decreases with age
		$n = 179$		

type and all of the published information has been based on cross-sectional data. Nevertheless, one may conclude that the trend seems to be for the auditory P300 to increase with age while the visual P300 decreases with advancing age during childhood and adolescence.

Based on cross-sectional observations of children at various ages, we first suggested that reduction in P300 amplitude seen in high-risk children may be due to a delay in a neurobiological dimension that is reflected in the P300 amplitude (Hill et al 1990; Steinhauer and Hill 1993). This hypothesis would predict that high-risk children would have age inappropriate levels of P300 (e.g., significantly lower auditory P300 than control children). Furthermore, longitudinal data have not previously been available to determine if the same child followed over time has varying developmental trajectories by modality and by risk group status.

Amplitude Versus Latency

There is a substantive literature demonstrating a relationship between prolonged latency of P300 and environmental exposures and between specific neuropathological states (e.g., Alzheimer's disease, closed head injury, and other organic brain syndromes) (Morrow et al 1992; Neshige et al 1988; Papanicolaou et al 1984; Polich 1989, 1991). In contrast to the increased latency seen in association with environmental exposures or organic disease states, decrements in P300 amplitude are more often associated with the presence of psychiatric disorders. Reduced amplitude has been reported for schizophrenic patients (Steinhauer and Zubin 1982; Steinhauer et al 1991; Pfefferbaum et al 1989) and patients diagnosed with depression (Bruder et al 1995; Blackwood et al 1987; Yanai et al 1997). Individuals selected for study because they carry an especially high loading for a particular psychiatric disorder, especially alcoholism (Begleiter et al 1984; Hill and Steinhauer 1993a; Steinhauer and Hill 1993; Friedman et al 1995; Hill et al 1995a), have been reported to show reduced amplitude when compared to controls. Thus, it is possible that the amplitude of the P300 component may be an inherent characteristic of individuals *before* they develop psychiatric states that may be related to their vulnerability for incurring these disorders (Hill et al 1987; Hill 1994).

Heritability of Alcoholism and of P300

There is substantial evidence that alcoholism has a familial/genetic basis. Based on twin, family and adoption studies, heritability of the liability for alcoholism is estimated to be about 50% (see Hill 1994 for review). P300 has been utilized as a potential risk marker for a number of psychiatric conditions, including alcoholism, in part, because there is evidence that a substantial portion of the variance in P300 can be explained by heritable factors. Thus, elucidating the factors responsible for variations in P300, particularly those that might be heritable, has been of interest given the observed association between P300 and psychopathological conditions. Overall, there is a considerable body of evidence suggesting that brain neuroelectrical activity, whether background electroencephalograms (Vogel et al 1979; Young et al 1972; Propping et al 1980; Lykken et al 1974), averaged sensory evoked responses (Buchsbaum 1974; Rust 1975), or ERP (Steinhauer et al 1987; Bock 1976; Surwillo 1980; O'Connor et al 1994; van Beijsterveldt 1996) is heritable.

A number of studies have reported that when ERP waveforms of two individuals are compared, greater concordance is observed between first-degree relatives than unrelated individuals, with the greatest similarity observed in monozygotic (MZ) twins (Steinhauer et al 1987; Bock 1976; Surwillo 1980; O'Connor et al 1994; van Beijsterveldt 1996; Hill et al 1999b). The van Beijsterveldt study found greater waveform similarity in MZ than DZ twins, with P300 amplitude highly correlated in twin pairs (between .5 and .9). Substantial correlations have been found in sibling pairs as well (Hill et al 1999b). Moreover, ERP data from our large family study of alcoholism have been analyzed using segregation analysis to determine possible modes of inheritance of the P300 component, with evidence presented for a major gene controlling the

Table 2. Gender and Wave Distributions

Number of assessments completed	High-risk		Low-risk		Total
	Male (n = 49)	Female (n = 41)	Male (n = 35)	Female (n = 31)	
Baseline/initial assessment	49	41	35	31	156
Retest 1	39	33	26	23	121
Retest 2	38	32	22	21	113
Retest 3	36	28	20	19	103
Retest 4	8	23	18	16	83
Retest 5	18	14	14	8	54
Retest 6	8	9	7	6	30

familial similarity in P300 amplitude (Aston and Hill 1990). Because there is evidence that P300 amplitude is heritable, it may be an especially useful marker of alcoholism risk in children who have not yet developed the disorder. Understanding the developmental course of P300 during childhood and adolescence, that may also be heritable, may be essential for using it as a risk marker for alcoholism and other psychiatric disorders.

P300 in Adult Alcoholics and High-Risk Children

ERP differences, especially in the amplitude of the P300 component, have been reported for male alcoholics when compared with control subjects (Porjesz et al 1987a, 1987b; Pfefferbaum et al 1991) though differences have not been found in all studies (Pfefferbaum et al 1979; Hill et al 1987, 1995b; Lille et al 1987; Hermanutz et al 1981). On the other hand, adult female alcoholics show profound reductions in P300 amplitude in comparison to age-matched normal controls (Hill and Steinhauer 1993b). Recent work suggests that reductions in female alcoholics may be due to the presence of comorbid depression (Hill et al 1999a).

At any rate, it is clear that a number of laboratories now have been able to document differences in P300 characteristics between high and low-risk children (Begleiter et al 1984; Hill and Steinhauer 1993a; Steinhauer and Hill 1993; Hill et al 1990, 1995a; Whipple et al 1988; Berman et al 1993). Because fewer than 200 children and adolescents have been assessed across available studies, and none have provided longitudinal follow-up data, the purpose of the present study was to directly assess the developmental delay hypothesis using the power of a longitudinal study design (Table 1). A secondary hypothesis was that children and adolescents who developed a psychopathological diagnosis some time during the observation window might have a different developmental trajectory. Finally, we hypothesized that risk status might interact with the presence of the psychopathological condition to produce varying growth trajectories of P300 amplitude.

Methods and Materials

Subjects

All available children between the ages of 8–18 who were offspring of parents enrolled in a large family study (Cognitive and Personality Factors in Relatives of Male Alcoholics, AA 05909-15) were included. A total of 156 children/adolescents participated in the study, a majority of whom participated in a longitudinal follow-up involving evaluation at approximately yearly intervals. The children were the available offspring of parents who came from either high-risk (HR) or low-risk (LR) families. A high-risk family was so designated based on entry criteria for inclusion of the family in the on-going family study. This included the presence of a minimum of two adult alcoholic brothers. The low-risk families were defined by the absence of alcoholism in the adult sibling generation, their parents, and grandparents.

Due to the highly selected nature of the high-risk and control families, children were entered into the study on the basis of availability, and thus, entered at different ages. A majority (75% HR and 61% LR) of the children entered the study between the ages of 8 and 12 so that the maximum number of follow-up evaluations could be obtained during adolescence, the point at which we hypothesized that critical neurobehavioral/neuroendocrine changes might influence developmental alterations in P300. The majority of the children completed 4 or more annual evaluations (Table 2). Some children completed as many as 7 separate evaluations. Over the course of the study, 18 children (8 high-risk and 10 low-risk) dropped out of the study for a loss of 11%. A total of 635 assessments were available for analysis (Table 3).

Clinical Assessment

All children were administered the Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS) (Chambers et al 1985) by trained (Masters level) interviewers. The parent who accompanied the child to the testing session participated in the K-SADS by providing answers to the same questions asked of the child. K-SADS interviewers had diagnostic reliability of 90% or greater with interviewers trained by the authors of the instrument. A resident (3rd or 4th year in an integrated child/adult psychiatry program) independently conducted an unstructured interview with both the child and the

Table 3. Distribution of Children Evaluated in Each Age Group

	High-risk		Low-risk		
Age	Male	Female	Male	Female	Total
7	0	1	1	0	2
8	14	11	8	7	40
9	12	9	5	6	32
10	18	19	14	11	62
11	19	24	12	13	68
12	22	24	16	11	73
13	17	18	19	15	69
14	24	24	21	10	79
15	22	20	18	11	71
16	18	14	15	16	63
17	12	10	11	9	42
18	13	4	7	10	34
Total					635

parent. A "best-estimate" consensus diagnosis was assigned for each child based on both the results of the K-SADS interview and the child psychiatrist's interview. Any discrepancies that arose were resolved in the presence of a third clinician. The interviewer and the psychiatrist were blind to the risk status of the subject's family. Statistical analyses were conducted for the presence or absence of the following selected disorders: depression, affective, phobia, anxiety, attention deficit/hyperactivity (ADHD), conduct, substance abuse/dependence, oppositional, and adjustment.

Event-Related Potentials—Auditory Procedure

Each child performed an auditory task during which ERPs were recorded. Before testing, subjects were given an audioscope screening test of 20 dBHL at frequencies of 500, 1000, 2000 and 4000 Hz. Results indicated that hearing was not impaired in any of the subjects.

The experiment consisted of a Choice Reaction Time task (RT), that has been employed previously (Hill and Steinhauer 1993a, b; Steinhauer et al 1987). This task is a modified version of the typical oddball paradigm. For the task, the subjects sat in a sound attenuated, darkened room and listened to "high" (1500 Hz) and "low" pitched (800 Hz) tones, presented every three seconds through a speaker placed in front of the subject. Before testing, subjects were required to identify "high" and "low" tones to ensure pitch differentiation. Tones were 40 msec in duration with an abrupt (2 msec) rise and fall time, at an intensity of 70 dBA. High and low tones were randomly generated by computer so that the overall probability of a high (infrequent) tone would be .25.

All subjects were told at the onset of testing that 1) the first tone they would hear on each block of trials would be a low tone, 2) there would be fewer high tones than low tones, and 3) two high tones would never occur in a row. To be sure that the task was understood, each subject was asked which tone would be heard after a high tone. All subjects responded correctly that a low tone would follow. Because we have demonstrated that the amplitude of the P300 is dependent on the conditional probability of two tones occurring in succession (Steinhauer et al 1987), we calculate the conditional probability of a high tone following a low tone to be 0.33 (the probability of a target divided by all possible unpredictable stimuli or .25/.75). The .33 probability condition was chosen for analysis as this is the probability condition producing the maximal P300 response as is the case for the "rare" condition in oddball tasks (Steinhauer and Hill 1993; Hill et al 1995a).

Subjects were asked to perform two blocks of 80 trials each. Subjects pressed one button when a high tone was heard and another button when a low tone occurred, alternating with each subject as to whether the left button first corresponded to a high tone or a low tone. On the second RT block, the subject was required to do the opposite. Responses were automatically encoded to determine accuracy. Each error-free block resulted in a reward of $0.25; $0.10 was given for each block with 1–2 errors (3 errors = no reward). Blocks with six or more errors were excluded from the analysis. All trials performed incorrectly were also discarded.

Visual Procedure

The visual event-related potential task employed was patterned after the procedure utilized by Begleiter et al (1984). Stimuli were presented on a color monitor using a 33 msec duration, with an intertrial interval varying randomly between 2.25 and 4 sec. One view, the non-target stimulus, was a simple circle to which the subject was instructed not to respond (blank condition). Additionally, the target condition consisted of one of four possible views of a head with a nose and only one ear. The subject was instructed to press the button that corresponded to the depicted ear. The easy condition occurred when the nose was oriented upward and the ear (right or left) was on the same side as the button depressed. In the hard condition, the nose was oriented downward and the subject was required to spatially rotate the head to respond correctly. Thus, in the hard condition, the ear was depicted on the opposite side of the head as the button pressed. Because previous reports (Begleiter et al 1984; Hill and Steinhauer 1993a) utilizing this paradigm have not found statistical differences between responses in the hard and easy conditions, we chose to analyze the hard condition only.

A standard set of instructions was read to each child. Before recording practice trials were presented at a longer display rate. Once the child was performing correctly (usually less than ten trials), the visual display duration was decreased to the 33 msec exposure time required for the main experiment for several additional practice trials. (The children were encouraged to respond quickly, but more importantly, to respond accurately.) Two blocks of 120 trials were presented to the subjects. Of the 240 total trials, 160 were blank (nontargets), 40 were easy condition targets (20 right, 20 left) and 40 were hard condition targets (20 right, 20 left).

Electrophysiological Recording and Peak Detection

ERPs were recorded using SensorMedic Ag/AgCl electrodes placed at midline frontal, vertex, parietal and occipital locations (Fz, Cz, Pz, Oz) as well as left and right parietal sites (P3, P4).

All active electrodes were referred to linked ears, with a forehead ground. Eye movement and blink artifacts were recorded by an additional electrode located under the left eye that also was referred to linked ears. All data were monitored online by an oscilloscope, and all trials affected by eye artifact were coded for exclusion (those exceeding 50 μV were rejected by preset software, a program laboratory coders could override where necessary). Data were digitized by a PDP 11/23 computer for 1200 msec at 125 Hz, beginning 200 msec before stimulus onset, and stored on magnetic media. Artifact free trials for each task were averaged for each condition and electrode.

In our laboratory, the P300 component is identified using an interactive computer algorithm that chooses the maximal amplitude (at Pz for P300) within a predefined latency window (264–424 msec). For the present analysis, our focus was solely on P300 amplitude and latency at Pz (the typical maximal response site for P300) because this component has been most strongly associated with alcoholism risk to date.

For the visual task, the P300 latency window was extended if necessary. Components were judged to be outside the latency range based on consensual agreement between two raters blind to each subject's family history. This is of particular importance because component latencies are typically longer in children than in adults, and are decreased for older children. Peak amplitude was computed as the deviation from the median voltage during the 200 msec prestimulus baseline, using the same time point for all electrode sites. Latency and peak to baseline amplitude data were automatically extracted and stored in ASCII files for subsequent analysis.

Utilizing a longitudinal data design, we analyzed the possible P300 amplitude and latency differences over time between high and low-risk children using latent growth curve modeling (significance set at $p \leq .5$). Using this method, each child's growth trajectory can be modeled. P300 amplitude growth or, alternatively, decline with age can be captured by random coefficients, known as latent variables in the latent curve analysis (Muthén and Curran 1997). Therefore, random coefficient growth curve models (with variable random effect design matrix across subjects, BMDP 5V) were chosen to analyze our longitudinal (up to 7 waves) data. Risk status (high-risk/low-risk) was specified as a grouping (between-subject) factor, that is a time-invariant covariate. The P300 amplitudes were viewed as repeated measures in our analysis. Linear and quadratic growth curve model fits were evaluated using the default Newton–Raphson algorithm to compute the maximum likelihood estimates.

Results

The children had participated in multiple assessments of psychopathology at approximately yearly intervals. These assessments were performed on the same test day that the P300 was assessed. Therefore, we could relate the risk status of the child determined by familial loading for alcoholism and the lifetime diagnosis of the child to the latent growth curves obtained for P300 amplitude and latency.

In one set of analyses, simply the presence or absence of any childhood diagnosis was used to classify subtypes of high and low-risk children and relate these subgroups to P300 amplitude. In another set of analyses, clinical data from each child were classified into one of four groups: none, internalizing disorder only, externalizing disorder only, or both externalizing and internalizing. Internalizing disorders included: depression, dysthymia, simple phobia, social phobia and anxiety disorders. Externalizing disorders included: conduct disorder, oppositional, attention deficit/hyperactivity disorder (ADHD), drug dependence or alcohol abuse/dependence. The effect of these classificatory groups was investigated with respect to P300 amplitude, ignoring risk status (Table 4).

Table 4. Distribution of Externalizing and Internalizing Diagnoses for High and Low-Risk Children

	High-risk		Low-risk		
Diagnosis	Male	Female	Male	Female	Total
No diagnosis	15	18	22	18	73
Externalizing only	12	9	2	1	24
Internalizing only	13	9	10	11	43
Externalizing and internalizing	9	5	1	1	16

Visual P300 Amplitude

Compared to the linear growth curve model, the quadratic model was a significantly better fit for the visual P300 amplitudes obtained for all of the children ($\chi^2 = 30.44$, df = 2, $p < .001$), for males only ($\chi^2 = 13.70$, df = 2, $p < .01$), and for females only ($\chi^2 = 20.70$, df = 2, $p < .001$). The close fit between the means of the grouped data (Table 5) and the theoretical growth curves may be seen for the visual paradigm in Figure 1. The quadratic growth curve obtained for the visual P300 shows a decrease in amplitude with age, with a stronger downward trend at later ages. Also, the quadratic growth curves differed significantly for high and low-risk males (Wald test

Table 5. Descriptive Statistics (Mean ± SE) for Visual P300 Amplitudes (μV)

	High-risk		Low-risk	
Age	Male	Female	Male	Female
8	28.32 ± 3.52	34.85 ± 2.48	40.63 ± 3.10	36.92 ± 1.94
9	28.60 ± 3.19	40.02 ± 3.47	43.73 ± 4.95	27.82 ± 5.15
10	30.63 ± 3.03	39.02 ± 3.26	36.43 ± 3.70	31.78 ± 3.26
11	28.79 ± 2.72	38.40 ± 2.22	34.53 ± 2.85	35.72 ± 4.18
12	28.63 ± 2.62	32.67 ± 2.00	32.23 ± 3.10	29.73 ± 2.99
13	28.06 ± 2.20	31.07 ± 2.38	34.12 ± 2.20	31.61 ± 1.49
14	25.54 ± 2.28	27.83 ± 2.10	30.11 ± 2.32	27.90 ± 1.64
15	21.42 ± 2.13	26.14 ± 2.24	27.09 ± 2.64	26.39 ± 2.09
16	21.57 ± 1.99	27.83 ± 3.03	20.83 ± 2.16	24.58 ± 1.38
17	20.60 ± 3.08	25.12 ± 3.59	21.92 ± 2.25	24.01 ± 2.45
18	18.70 ± 2.08	25.11 ± 5.95	23.03 ± 2.77	22.05 ± 1.60

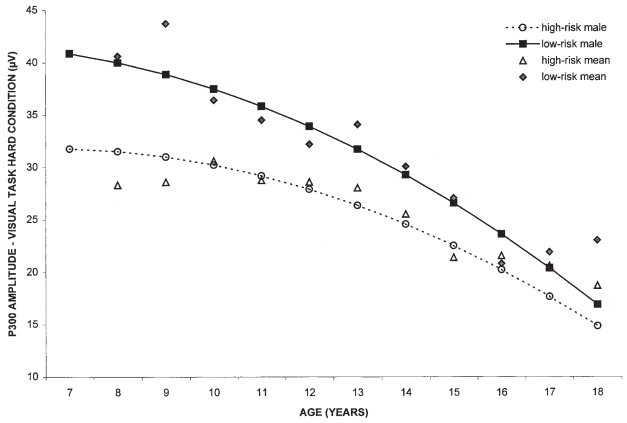

Figure 1. Quadratic growth curve of visual P300 amplitude obtained for high and low-risk males. High-risk males had lower P300 amplitude than low-risk males and displayed a slower rate of change with age than did the low-risk males. Note the closeness of fit between the means of the grouped data and the theoretical growth curves.

statistic $\chi^2 = 341.89$, df = 1, $p < .0001$) and for high and low-risk females ($\chi^2 = 60.48$, df = 1, $p < .001$). High-risk boys had lower P300 amplitudes and a lesser rate of change in amplitude than low-risk boys. Contrary to prediction, the high-risk girls had higher P300 amplitudes than did the low-risk girls, with a significantly faster rate of change in amplitude with age. When childhood psychopathology was considered, a much different pattern emerged for the girls. Utilizing a four group analysis based on risk status (high-risk or low-risk) and psychopathology (presence or absence of a lifetime diagnosis), a significant difference among the groups was seen ($\chi^2 = 11.61$, df = 3, $p = .01$). Analysis of amplitude data for specific age groups showed a

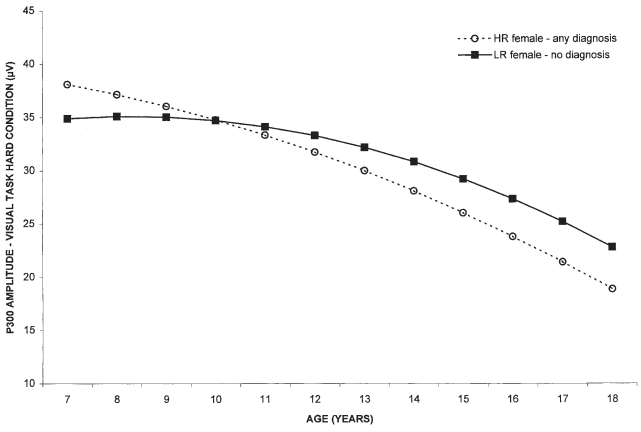

Figure 2. High-risk girls with any childhood diagnosis and low-risk girls with no diagnosis are plotted to illustrate the effect of two risk markers: high or low-risk status and presence or absence of any psychiatric diagnosis in childhood on visual P300 in girls. The high-risk females with a diagnosis had significantly reduced P300 amplitude compared to controls without a diagnosis.

Table 6. Descriptive Statistics (mean ± SE) for Auditory P300 (Choice Reaction Task) Amplitudes (μV)

	High-risk		Low-risk	
Age	Male	Female	Male	Female
8	10.28 ± 1.71	18.83 ± 2.55	14.14 ± 2.42	15.42 ± 2.17
9	17.44 ± 2.11	25.32 ± 5.42	17.14 ± 2.57	15.96 ± 2.03
10	19.00 ± 2.07	24.83 ± 2.50	22.32 ± 2.62	18.42 ± 2.55
11	16.21 ± 1.25	28.38 ± 1.88	21.26 ± 1.84	21.43 ± 3.00
12	18.18 ± 1.22	27.24 ± 2.02	23.92 ± 2.79	23.60 ± 2.67
13	19.91 ± 1.72	27.28 ± 1.59	23.44 ± 1.62	23.33 ± 2.21
14	21.12 ± 1.77	24.52 ± 1.72	25.82 ± 1.88	25.38 ± 3.24
15	21.02 ± 1.08	24.45 ± 2.19	22.25 ± 1.81	23.36 ± 1.97
16	21.66 ± 1.86	26.27 ± 2.52	22.10 ± 1.75	22.83 ± 1.33
17	22.50 ± 2.62	22.40 ± 2.39	22.47 ± 1.60	23.46 ± 1.45
18	18.75 ± 2.07	23.16 ± 5.35	25.02 ± 3.29	22.72 ± 2.62

significant reduction in amplitude for high-risk girls relative to control girls when the groups were tested at ages 13 through 18 (p values between .02 and .05). Further, as may be seen in Figure 2, the high-risk girls with any diagnosis did show a developmental delay along with an accelerated rate of change starting at around the onset of adolescence ($\chi^2 = 3.90$, df = 1, $p = .05$). Therefore, boys appear to be developmentally delayed in association with risk status alone, whereas for girls, the presence of lifetime psychopathology must be considered along with risk status to see the reduction in amplitude.

Auditory P300 Amplitude (Choice Reaction Task)

Data obtained from the Choice Reaction Task were analyzed to determine the best fit with age. Similar to the results obtained for visual P300 amplitude, the quadratic growth curve models fit the auditory P300 data well (Table 6) for all children ($\chi^2 = 44.08$, df = 2, $p < .001$), for males ($\chi^2 = 64.86$, df = 2, $p < .001$), and for females ($\chi^2 = 23.62$, df = 2, $p < .001$). As may be seen in Figure 3a, Wald tests of significance showed that high-risk boys and low-risk boys had significantly different quadratic growth curves ($\chi^2 = 1095.21$, df = 1, $p < .0001$). Also, as predicted from earlier studies (Hill et al 1990, 1995a; Steinhauer and Hill 1993), high-risk boys had smaller P300 amplitude than low-risk boys. Additionally, the high-risk boys showed a lesser rate of change in amplitude with age than did the low-risk boys. This is consistent with the notion that high-risk boys may be developmentally delayed with respect to the normal growth curves obtained for low-risk boys.

The pattern found in boys was not found for girls, however (Figure 3b). Overall, no significant differences in the quadratic growth curves were found between high and low-risk girls, and as a group, the high-risk girls appeared to have larger auditory P300 amplitudes than low-risk girls,

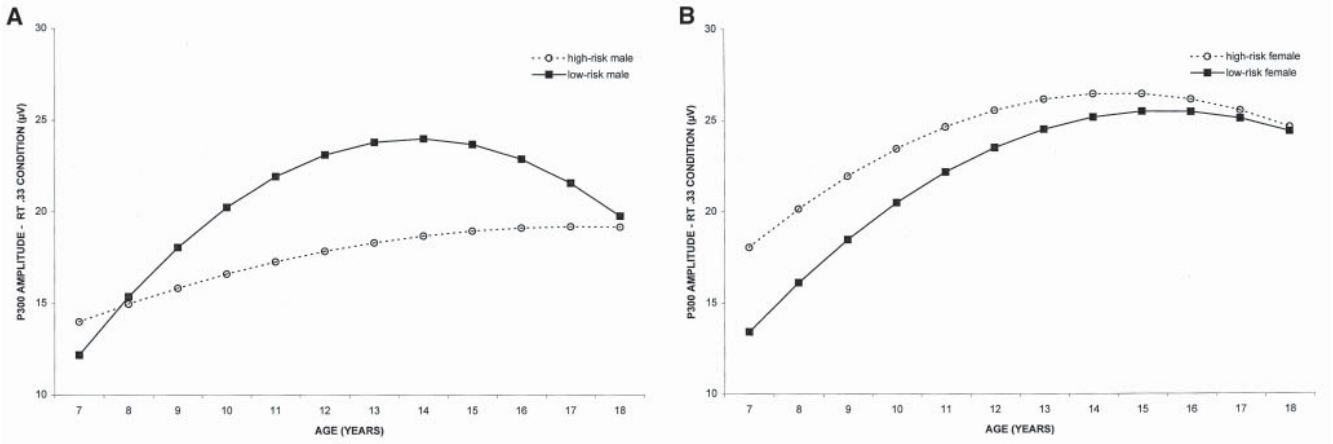

Figure 3. (A) The quadratic growth curves for male high and low-risk children/adolescents are plotted. Note the reduced amplitude and slower rate of change observed in the male high-risk individuals in the auditory task. (B) The quadratic growth curves for female high and low-risk individuals illustrate the increasing P300 amplitude with age. Note that the high-risk girls have increased auditory P300 amplitude.

though not significantly larger. Also, this pattern was not altered by using psychiatric diagnosis of the child as a possible explanatory variable.

It has been suggested that P300 amplitude might reflect changes in head size during development (Polich et al 1990). We reasoned that changes in body size with growth (height and weight) might be used as an approximation of change in head size during childhood and adolescence. Therefore, data were analyzed using quadratic models with two time-varying covariates, height and weight. No significant differences in growth trends for either height or weight were found between the high-risk and low-risk children. Moreover, the difference in the P300 amplitude quadratic trends seen for the high-risk and low-risk boys remained significant when height and weight were used as covariates. Thus, we conclude that the significant difference in auditory P300 amplitude found for the high and low-risk children was not due to overall changes in body growth, and by inference, head size.

Visual P300 Latency

Compared to the quadratic model, the linear growth curve model was a significantly better fit to the latency data ($\chi^2 = 22.87$, df = 2, $p < .001$) for all children. A comparison of growth functions (see Figure 4a) for the high and low-risk children indicated no significant difference in the growth functions for the two groups ($\chi^2 = 0.55$, df = 1, $p = .46$).

Auditory P300 Latency

The latency data were fit to both the quadratic and linear models, with the linear model providing the best fit ($\chi^2 = 25.39$, df = 2, $p < .001$; see Figure 4b). Comparison of the latency data obtained for high and low-risk groups as a

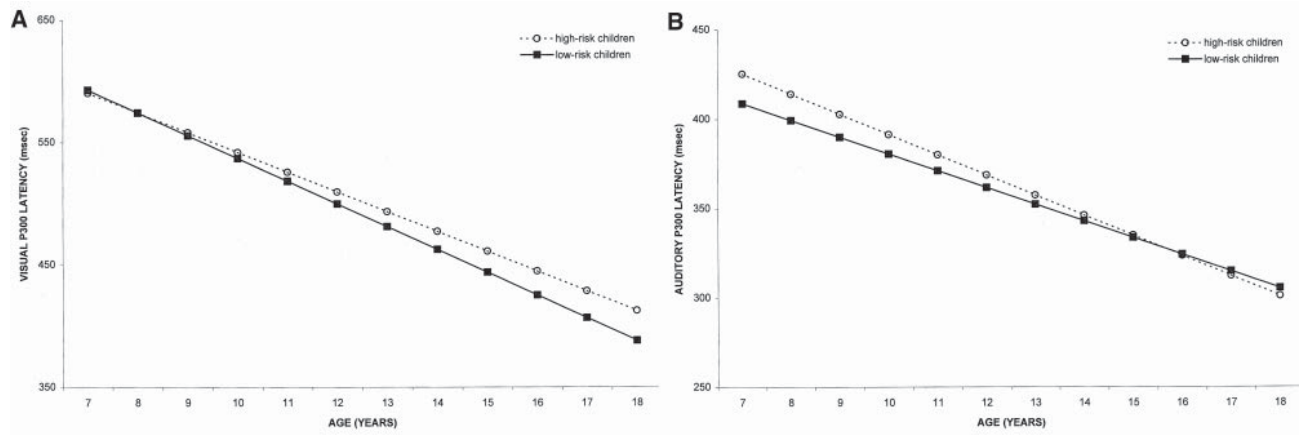

Figure 4. (A) Visual P300 latency is displayed as a function of age. The data show a significant downward linear trend with age. No significant differences by risk group were seen. (B) Auditory P300 latency shows a significant downward linear trend with age. No significant differences by risk group were seen.

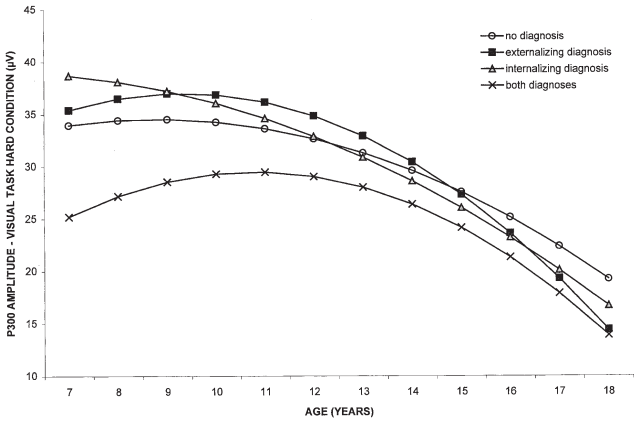

Figure 5. The effect of having either an internalizing or externalizing disorder, or both, during childhood is displayed for the entire group of male and female children/adolescents without respect to risk status. Note that having both internalizing and externalizing disorders appears to have a cumulative effect on reducing the visual P300 amplitude.

whole indicated no significant difference in latency with age ($\chi^2 = 0.71$, df = 1, $p = .40$). A difference in the age-related changes in latency by risk group was found for the girls ($\chi^2 = 4.82$, df = 1, $p = .03$), with the high-risk girls having significantly longer latency between the ages of 7 and 13.

Visual P300 Growth Curves and Childhood Diagnosis

An overall analysis of lifetime psychopathology was completed for all children and again separately for each gender. Here, quadratic coefficients were determined and the curves plotted for each of the diagnostic groups (no diagnosis, internalizing only, externalizing only, or both internalizing and externalizing), ignoring risk status (it should be noted that significantly more high-risk children have one or more diagnoses than do low-risk children.) As may be seen in Figure 5, the children without evidence of ever having a lifetime psychiatric disorder showed a significantly different rate of change in P300 with age than did the children who had both an internalizing and externalizing disorder (comparison of confidence intervals revealed significance at $p \leq .05$). Also, the internalizing group was significantly different than the group with both internalizing and externalizing disorders. When the results were further analyzed by gender (Figures 6a and 6b), it may be noted that children with both internalizing and externalizing disorders were significantly different from those with either internalizing alone or externalizing alone. This suggests that the more children are afflicted with multiple disorders the more likely they are to have reduced P300 in childhood and to show a slower growth trajectory in P300 amplitude than children with no disorders. Also, it should be noted that both visual and auditory P300 is reduced in high-risk boys, accompanied by a slower rate of change from childhood to adolescence. This pattern is seen without considering the additional risk factor of having a childhood psychiatric disorder. In contrast, high-risk girls showed visual P300 reduction, but only when the presence of any diagnosis was considered.

Discussion

This study documents the developmental course of P300 amplitude and latency from early childhood to late adolescence. The major age-related changes were: (1) Both visual and auditory P300 amplitude changed with age, with a quadratic growth curve providing the best fit to the

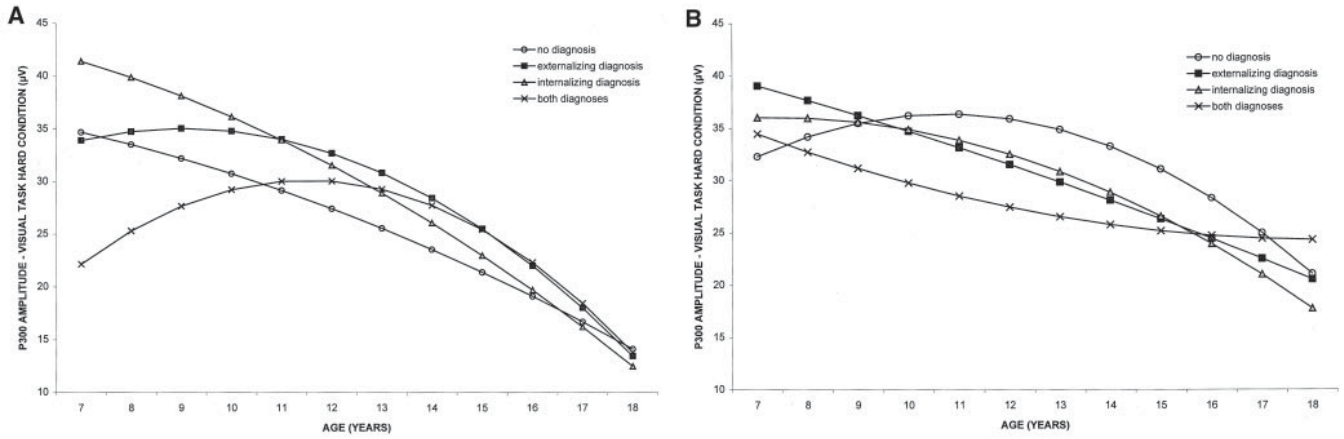

Figure 6. (A) The effect of having either an internalizing or externalizing disorder, or both, during childhood is displayed for all male children without respect to risk status. (B) The effect of having either an internalizing or externalizing disorder, or both, during childhood is displayed for all female children without respect to risk status.

data; (2) visual P300 amplitude tended to decrease with age while auditory P300 amplitude tended to increase; (3) both visual and auditory P300 latency became shorter with age.

We examined the hypothesis that the reduction in P300 amplitude so often seen in high-risk children (Begleiter et al 1984; Hill and Steinhauer 1993a; Steinhauer and Hill 1993; Hill et al 1995a) from alcoholic families might be due to a developmental delay in P300 amplitude. Under this hypothesis, we expected that the rate of change in P300 amplitude with age would vary by risk group status. It is important to note that it was necessary to first determine the direction of "normal" change by assessing age-related changes separately by modality. Utilizing a longitudinal design involving a total of 635 separate assessments, it was possible to determine that the direction of normal change varied across modalities. The major findings with respect to risk group differences were: (1) the high and low-risk groups show convergence in P300 amplitude for both the visual and auditory modalities with the theoretical point of convergence being at age 18 for the auditory condition and age 22 for the visual paradigm; (2) latent growth curves describing visual P300 revealed that male high-risk children had both lower P300 amplitude and a lesser rate of change with age than that seen in low-risk boys; (3) the latent growth curves describing auditory P300 similarly revealed that male high-risk children had both lower P300 amplitude and a lesser rate of change with age; (4) no significant differences in the auditory quadratic growth curves were seen for the high and low-risk girls; (5) the quadratic growth curves describing the visual P300 for the high and low-risk girls were significantly different, with the high-risk girls having a faster rate of growth due to the fact that up to the time of puberty (ages 9–13), the high-risk girls as a group actually have significantly higher P300 amplitude than do low-risk girls. Further analysis by childhood diagnostic status indicates the presence of admixture in P300 amplitude among HR girls. Those girls who had a childhood diagnosis displayed reduced P300 amplitude relative to control girls without a diagnosis; (6) the growth curves for visual P300 obtained from high and low-risk children were greatly influenced by the presence of childhood psychiatric disorders.

The present results are consistent with previous reports concerning the developmental course of P300 amplitude and latency, though previous results have been obtained using solely cross-sectional designs. Previous reports have indicated that auditory P300 amplitude tends to grow larger with age during childhood and adolescence (Ladish and Polich 1989; Polich et al 1990) while visual P300 amplitude tends to decrease with age during this same period (Courchesne 1977, 1978). Why the developmental course varies so radically during childhood and adolescence is currently unknown. It is known that the primary and secondary visual areas are peculiar in that they attain a stable, adult thickness between 6 and 15 months of age (Rabinowicz et al 1977).

Based on the converging P300 amplitudes of the high and low-risk groups by late adolescence, the present results are not consistent with reports of decreased amplitude in adult alcoholics and their adult high-risk relatives (Porjesz et al 1998). Based on an analysis of 217 ERP records, we have previously reported no differences in auditory P300 amplitude in adult male alcoholics and their adult high-risk relatives in comparison to controls (Hill et al 1995b). Moreover, unpublished data based on 189 visual ERP recordings from our laboratory revealed no difference among adult female alcoholics and controls when the presence of comorbid depression was taken into account (Hill et al, submitted). We hypothesize that the genetic vulnerability to alcoholism, that is carried by high-risk children and is manifest in lower P300 amplitude in childhood, normalizes by adulthood. Should this be the case, P300 can still be used in children as a discriminating marker of risk for later development of alcohol problems. We suggest that when reduced P300 is seen in adult alcoholics and their adult high-risk relatives compared to adult controls, it is not due to the underlying P300 abnormality these individuals may have had in childhood, but rather to the presence of comorbid psychiatric conditions such as depression present in adulthood.

The results obtained for age-related changes in latency are consistent with previous reports in which children/adolescents of a similar age range showed reduction in latency with age in both the auditory (Polich et al 1985; Pearce et al 1989) and visual conditions (Courchesne 1977, 1978). In the present study latency was also analyzed with respect to risk group differences. Consistent with previous studies from our laboratory (Hill and Steinhauer 1993a; Steinhauer and Hill 1993; Hill et al 1995a), we found no differences in latency by risk group overall. We did find longer auditory P300 latency in high-risk girls as a group.

A secondary goal was to determine if childhood psychopathology might influence the developmental course of P300. We hypothesized that the appearance of psychopathology at any time during the window of observation might reveal different developmental trajectories. The question asked was not what the concurrent effect of psychopathology was on P300, but rather would the existence of an internalizing or externalizing disorder during childhood or adolescence alter the P300 growth trajectory. Several previous cross-sectional studies have shown that psychopathological states influence the amplitude of P300 both in children/adolescents (Courchesne 1984; Lincoln and Courchesne 1985; Holcomb et al 1985)

and in adults (Bruder et al 1995; Steinhauer et al 1991; Blackwood et al 1987). The developmental course of P300 has not previously been assessed with respect to the presence of psychopathological conditions. In pursuing this type of analysis, we had to make certain assumptions. First, though we could see changes in diagnostic status of the child at yearly intervals and could utilize the onset or offset of an illness in relation to amplitude of the P300, this could not be done in the context of the latent growth curve analysis. Therefore, we chose to classify each child on the basis of whether they had ever received a diagnosis that would fall within the internalizing or externalizing domains. Utilizing this method of classification, we find that the amplitude of the P300 shows a graded response to psychopathological conditions, with the amplitude being lower for those with either internalizing or externalizing disorders compared to those with no diagnosis, and with the greatest reduction in amplitude and the slowest rate of change being seen in persons with both types of disorders.

In conclusion, longitudinal data involving 635 annual assessments over an 8-year-period allowed us to conclude that the developmental course of P300 varies considerably from childhood through adolescence to young adulthood. Important differences exist by modality and gender for both P300 amplitude and latency. Moreover, psychopathology appearing at any time during childhood/adolescence alters the shape of the P300 growth curve so that this variable must also be taken into account when assessing the likelihood that a particular ERP component is or is not a good candidate as a risk marker. Knowledge of these developmental trajectories is critical to our understanding of possible differences between children who are at high and low risk for developing alcoholism. It would appear that P300 remains a good candidate for "risk marker" status in children. Previously, reduced P300 amplitude has been shown to predict outcome after a 4-year follow-up (Berman et al 1993) and an 8-year follow-up in a small pilot study (Hill et al 1995c). Whether or not reduced P300 will specifically predict later development of substance dependence or is a marker for adult psychopathology is currently unknown. Squires-Wheeler et al (1993), in a ten year follow-up of children at high risk for schizophrenia, found that reduced P300 at age 15 predicted overall Global Personality Functioning though not schizophrenia. Whether the failure to see an association with schizophrenia means that the reductions in P300 seen in adult schizophrenics cannot be seen in childhood or is rather due to low base rate of schizophrenia is unknown. Nevertheless, that study provided important insight into the role of P300 in childhood for predicting problems with adult adjustment. Quite possibly P300 reduction is a risk marker for adult psychopathology. The prediction of which psychiatric disorder will be seen in adulthood may be determined by the particular familial loading for specific psychiatric disorders each child has inherited. Knowledge of the presence or absence of psychiatric disorders in childhood provides an additional risk factor that may be especially useful in girls.

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