

# A Simple Auditory Oddball Task in Young Adult Males at High Risk for Alcoholism

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The reduction in the amplitude of the auditory P300 in young adult males at high risk for alcoholism has not been as consistently replicated as has been the reduction in the visual P300 amplitude in the same group. The easier nature of the auditory task was thought to be responsible for the inconsistency. We examined the auditory P300 amplitude in a group that has not yet been studied, young adult sons of alcoholics (mean age = 24.9 years,  $n = 48$ ), and compared them with age and sex-matched controls (mean age = 27.8 years,  $n = 23$ ). We found the auditory P300 amplitude to be reduced in the high-risk group and this reduction to be the greatest over the posterior centroparietal and occipital areas when individual leads were examined. We further analyzed the data using current source density, a mathematical transformation that circumvents some of the errors inherent in measuring scalp-evoked potentials, and found reduced current source density in the high-risk group in the posterior central and parietal areas. Thus, we found that a simple auditory oddball task was effective in eliciting P300 differences in groups at high and low risk for alcoholism. The clinical significance of the P300 is discussed, as well as the relevance of task difficulty in eliciting auditory P300 differences in young males at high risk for alcoholism.

**Key Words:** Auditory P300, High-Risk Males, Alcoholism, Current Source Density.

NUMEROUS EVENT-related potential (ERP) studies have reported reduced visual P300 amplitudes in males at high risk for alcoholism.<sup>1-4</sup> The reduction in auditory P300 amplitudes in the same group has been less uniformly replicated. Although some laboratories have found a reduction in the auditory P300 amplitude in males at high risk for alcoholism,<sup>5-7</sup> other laboratories have not been able to replicate this finding.<sup>8</sup> Task difficulty has been postulated as one explanation for the discrepancy among laboratories.<sup>8</sup>

In a recent extensive meta-analysis of P300 amplitude in males at risk for alcoholism, Polich et al.<sup>8</sup> concluded that, whereas individuals with a family history of alcoholism demonstrated lower P300 amplitudes compared with individuals without a family history, these results were most consistent in the visual paradigm. They postulated that the

auditory and visual paradigms may not have had comparable levels of task difficulty and that the more difficult visual tasks were better at eliciting P300 differences, compared with the easier auditory paradigms. This conclusion is supported by Whipple et al.'s<sup>9</sup> finding that complex visual tasks were better than simple visual tasks at eliciting P300 reductions in high-risk males, compared with controls.

However, when O'Connor et al.<sup>10</sup> analyzed visual ERPs in young adult males at high risk for alcoholism, they found lower P300 amplitudes for both simple and complex tasks, compared with controls. Also, Porjesz and Begleiter<sup>3</sup> found that the largest differences in P300 amplitude between groups occurred in response to the easy target, to which controls exhibited maximal voltages with the most significant differences at Cz and Pz. Thus, the case for task difficulty and its bearing on the P300 amplitude remains to be made.

Whereas the ERP is an index of electrophysiological activity within the brain, its measurement presents some problems. Recorded from a finite number of sources, the ERP is contaminated by sources distant from the recording site because of the process of smearing, the inability to provide an inactive reference, and the volume conductor effects of the brain and its coverings, which further modify the ERP.<sup>11</sup> To circumvent these problems, a mathematical transformation has been used. Using the Spline Laplacian method,<sup>11,12</sup> simultaneously recorded values from all the scalp electrodes are used to provide a derived value for the current source density (CSD) distribution on the scalp. Thus, the CSD is more precise than the ERP in reflecting the electrical activity under the scalp.

Our study was undertaken to determine whether there were any differences in the P300 amplitude in young adult males at high risk for alcoholism, compared with low-risk males using an easy auditory oddball paradigm. We also attempted to more precisely ascertain possible topographical differences between high-risk and low-risk individuals using CSD measures. Finally, we speculate on the significance and possible clinical implications of our results.

## METHODS

### Subjects

The subjects in this study were 71 young adult, nonalcoholic males. The low-risk group ( $n = 23$ , mean age = 27.8 years,  $SD \pm 3.93$  years) was recruited either through newspaper ads or notices posted in the Health Science Center. The initial screening procedure required each prospective

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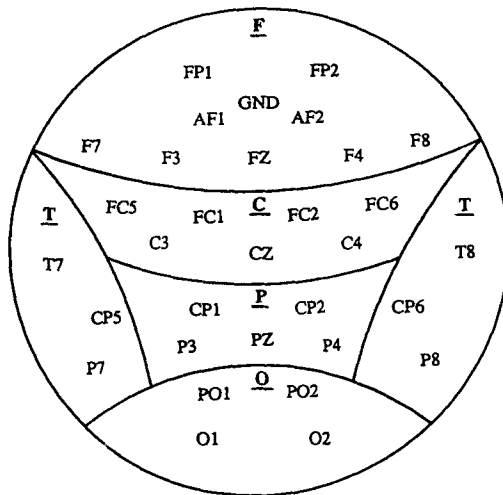


Fig. 1. Regional grouping of electrodes. F, frontal; C, central; T, temporal; P, parietal; O, occipital.

subject to fill out a questionnaire detailing alcohol/drug use, and medical and psychiatric histories for both himself and his relatives. Inclusion in this group depended on both the responses to the questionnaire and the requirement that none of the low-risk subjects first- or second-degree relatives be diagnosed as alcoholic.

The high-risk group ( $n = 48$ , mean age = 24.9 years,  $SD \pm 4.87$  years) consisted of young adult, nonalcoholic males recruited using the same methods detailed herein. Inclusion in the high-risk group required that at least the subject's father be classified as alcohol-dependent (DSM-III-R). However, if the mother of an individual was alcoholic, that individual was excluded from the study to rule out the effects of fetal alcohol syndrome and fetal alcohol effects.

Each individual in both groups was required to give informed consent and was paid for his services. Exclusionary criteria for both groups included major medical problems, a current requirement for medication with effects on the central nervous system, or a history of psychiatric problems and/or drug and alcohol abuse. Upon meeting these criteria, each subject was assessed at the laboratory where he underwent a detailed interview (by B.P. or H.B.) focusing on questions concerning drug, alcohol, medical, and psychiatric history for both first- and second-degree relatives. All subjects were asked to abstain from alcohol for 48 hr before testing. A breathalyzer test was administered to all subjects on the day of testing, and those with values greater than zero were not used in the study.

#### Experimental Design

The subject was seated comfortably in a dimly lit, temperature-regulated, sound-attenuated chamber (Industrial Acoustics Corporation). He was told to keep his eyes focused on a fixation target centrally displayed on a computer monitor (Concurrent Computer Corporation). Each subject wore a fitted electrode cap (Electro-Cap International, Inc.) containing either 31 or 61 electrodes. Nineteen high-risk subjects underwent 61 channel recordings, and the remainder of the subjects underwent 31 channel recordings. Data from the 61 channel recordings were converted into 31 channel recordings for the purpose of data analyses. Figure 1 presents the recording electrode montage and the regional electrode groupings used for the statistical analyses. The nasion served as reference and the forehead as ground. Both vertical and horizontal eye movements were monitored. EEG activity was amplified 10K (Sensorium EPA-2 Electrophysiology Amplifier; bandpass 0.02–50 Hz). EEG activity was continuously sampled at a rate of 256 Hz, beginning 187 msec before stimulus presentation (baseline) and continuing until the next stimulus (1.5 sec). The ERPs to each stimulus presentation were monitored. Subjects were warned not to blink their eyes and to sit still. Both digital filtering (32-Hz low-pass) of the raw data and artifact rejection (electro-

myogram, electro-oculogram, and saturation artifact  $> 73.3 \mu V$ ) were performed.

The two binaurally presented stimuli consisted of a 600-Hz (low) tone and a 1600-Hz (high) tone produced by a tone generator designed and constructed on site (Scientific and Medical Instrumentation Division, HSCB). Each stimulus had a 60-msec duration (10-msec rise and fall time, 40-msec plateau) and an intensity level of 60 dB SPL. A computer (Concurrent Computer Corporation) initiated the stimuli with a uniform interstimulus interval of 1.5 sec. The rare and frequent tones had 0.125 and 0.875 probabilities of occurrence, respectively. The designation of the low or high frequency tone as the rare stimulus was alternated across subjects. The auditory stimuli were presented binaurally through headphones (Ety-motic Research, model ER-3A TubePhone Insert Earphones, 50 ohms impedance), in which the earpiece and a short length of the TubePhone were fitted under the electrode cap, and the individual left and right transducer cases were situated on either side of the neck. When the subject detected the rare tone, he depressed a button on a modified computer mouse as quickly as possible with the index finger of his dominant hand. This action terminated a clock started at stimulus onset and defined the response time (RT). The subject received a maximum of 400 trials, but the experiment could be terminated after as few as 100 artifact-free trials (a minimum of 25 target and 75 nontarget trials) were acquired. Response speed was emphasized, but not at the cost of accuracy. Trials with RT  $> 1000$  msec were rejected. The ERPs and RTs from the accepted trials were automatically placed in 1 of 2 categories for subsequent summation, averaging, and statistical analyses.

#### Data Analysis

For each subject, the target ERPs were analyzed via an automatic peak detection program. The P300 component was selected as the largest amplitude peak within a time window from 250 to 500 msec. Thus, each subject's data consisted of peak voltages ( $\mu V$ ) and latencies (msec) at each electrode. ERP data were analyzed for specific electrodes and regional groups of electrodes, because we wished to evaluate both individual and regional differences in ERPs between the high-risk and low-risk groups.

Five regional groupings of the 31 electrodes were created to evaluate ERP characteristics by region: *frontal*—FP1, FP2, AF1, AF2, F3, F4, F7, F8, Fz; *central*—FC5, FC6, FC1, FC2, C3, C4, Cz; *parietal*—CP1, CP2, P3, P4, Pz; *temporal*—T7, T8, CP5, CP6, P7, P8; and *occipital*—PO1, PO2, O1, O2 (Fig. 1). Multivariate analysis of variance (MANOVA, SAS version 6) was used to assess group differences in P300 amplitude and latency in each of the aforementioned regions. Univariate analysis of variance (ANOVA, SAS version 6) was used to analyze differences in P300 amplitude and latency for individual electrodes between the high-risk and low-risk groups.

Two tailed  $t$  tests for independent groups were used to evaluate differences between high-risk and low risk groups in RT, ages, and drinking behavior. The number of drinks per occasion and the number of drinks per month for each subject were used to determine differences in alcohol consumption between groups. A drink was defined as 12 oz of beer, 4 oz of wine, a single shot, or a single mixed drink. The effect of the number of drinks per day and the number of drinks per month for each subject was analyzed using these values as covariates in the MANOVA for regional differences and in the ANOVA to analyze individual lead differences. The mean family density of alcoholism among the high-risk subjects was determined. Regional topographic differences between both groups were also assessed using CSD measures.

## RESULTS

The regional MANOVA analyses of the P300 characteristics in the target condition demonstrated significant P300 amplitude reductions in the high-risk group for 2 of the 5 regions: frontal ( $p < 0.010$ ) and occipital ( $p < 0.002$ ). There were no significant differences in the central and

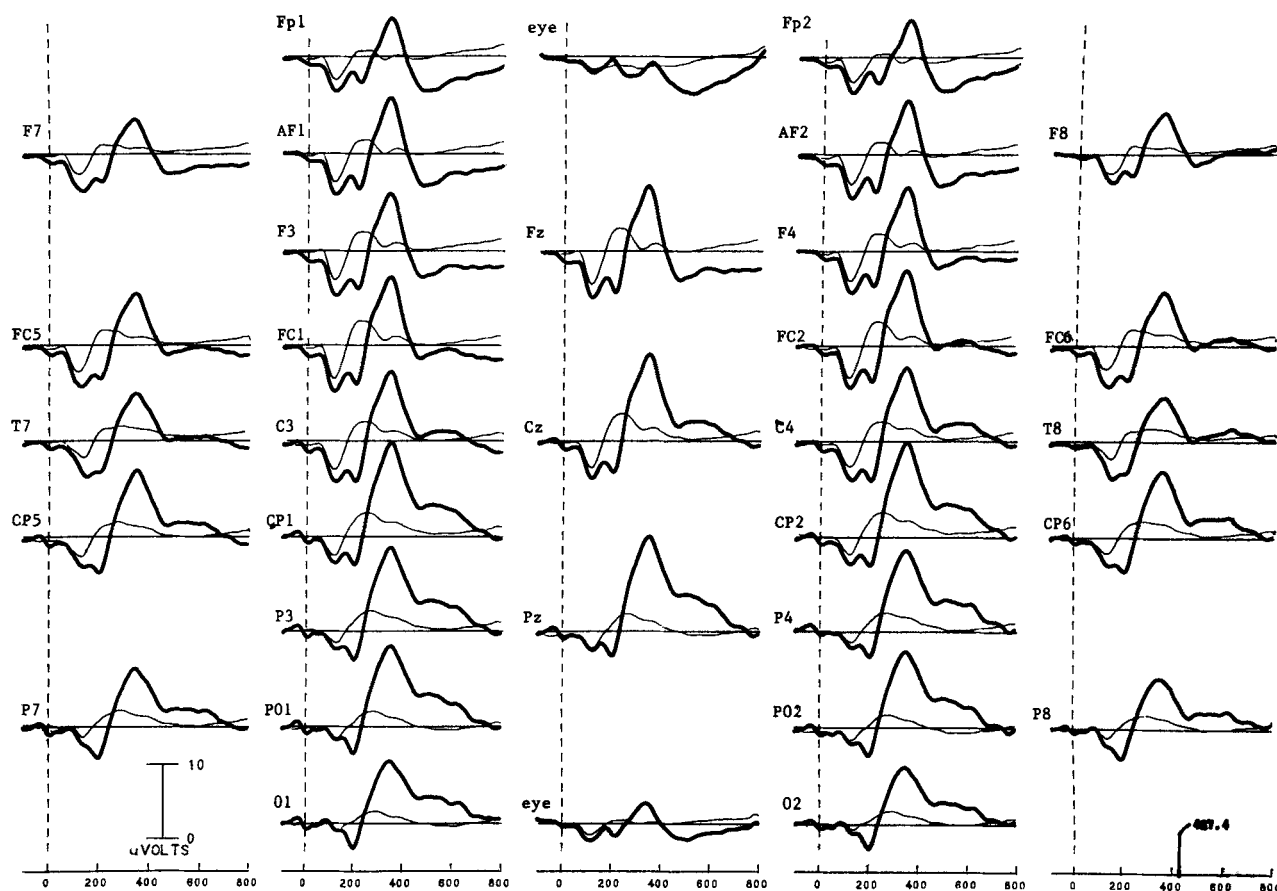


Fig. 2. Grand mean graph of ERP for high-risk group rare (target; bold line) versus frequent (nontarget; light line) stimulus.

parietal regions using MANOVA. However, ANOVA analysis of ERPs from individual leads showed significant P300 amplitude reductions in the high-risk group for the following 12 leads: P3 ( $p < 0.019$ ), P4 ( $p < 0.008$ ), Pz ( $p < 0.008$ ), P8 ( $p < 0.044$ ), CP2 ( $p < 0.017$ ), CP1 ( $p < 0.021$ ), C4 ( $p < 0.023$ ), Cz ( $p < 0.036$ ), CP6 ( $p < 0.028$ ), PO1 ( $p < 0.008$ ), PO2 ( $p < 0.008$ ) and O2 ( $p < 0.035$ ). (See Figs. 2 and 3 for grand mean graphs of ERPs for both groups, and Fig. 4 for histogram of P300 amplitude at Pz for both groups.) The lack of group ERP centroparietal differences in the presence of clear individual ERP differences in the same region is because of the high variance in the ERPs in the centroparietal region.

There were no significant differences in mean RT or ages between the groups. There were no significant differences in the latency of the ERP between the groups at any lead. The mean family density of alcoholism among the high-risk subjects (including the subject's father) was 2.8 (SD = 1.50; range = 1–7).

The mean number of drinks per month was 28.7 for the high-risk group and 9.3 for the low-risk group ( $p < 0.005$ ). The mean number of drinks per occasion was 3.6 for the high-risk group versus 1.9 for the low-risk group ( $p < 0.008$ ). Because of the significant differences in drinking behavior between the groups, the ERP data were subjected to separate MANOVAs and ANOVAs using drinks per

occasion and drinks per month as covariates. The MANOVAs of the regional ERP retained significance in the frontal and occipital areas using either drinks per occasion (frontal,  $p < 0.029$ ; occipital,  $p < 0.003$ ) or drinks per month (frontal,  $p < 0.015$ ; occipital,  $p < 0.003$ ) as a covariate. When the ERP data from the individual leads were analyzed by ANOVA, the same four leads showed significant ERP reductions in the high-risk group using either drinks per occasion (P4,  $p < 0.030$ ; Pz,  $p < 0.031$ ; PO1,  $p < 0.029$ ; PO2,  $p < 0.030$ ) or drinks per month (P4,  $p < 0.030$ ; Pz,  $p < 0.032$ ; PO1,  $p < 0.029$ ; PO2,  $p < 0.030$ ) as a covariate.

Visual assessment of CSD suggests stronger sources in the low-risk group compared with the high-risk groups (Fig. 5). The areas of greatest reduction of CSD in the high-risk group are in the posterior central, parietal, and occipital areas bilaterally and the right frontal area. Within the high-risk group, the right hemisphere shows more reduction in CSD when compared with the left hemisphere. The CSD findings are consistent with the findings of the ANOVA analysis of individual ERP leads.

## DISCUSSION

It has been demonstrated by various laboratories, including our own, that the visual P300 amplitudes are reduced in

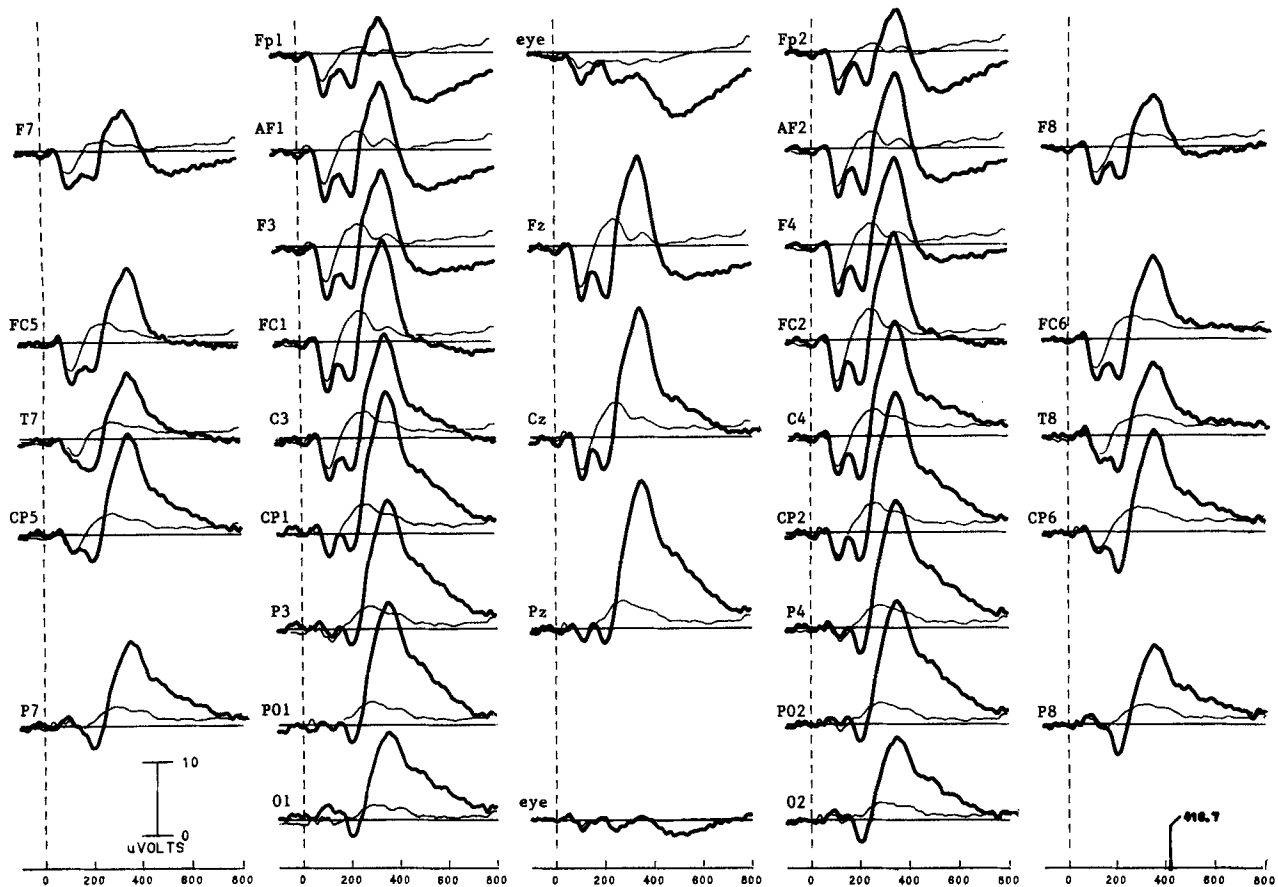


Fig. 3. Grand mean graph of ERP for low-risk group rare (target; bold line) versus frequent (nontarget; light line) stimulus.

individuals at high risk for developing alcoholism.<sup>1-4,10,13</sup> The auditory P300, however, has been less extensively studied and predominantly in children under the age of 18 in the high-risk population.<sup>1,6-8</sup> These studies have shown that the P300 amplitude is reduced in high-risk children in the auditory paradigm. Our study examined the differences in auditory P300 amplitudes in young adult males (mean age = 24.9 years) with and without a family history of alcoholism, and found the auditory P300 amplitude to be significantly reduced in those with a positive family history. Regionally, these differences in P300 amplitude were statistically significant in the frontal and occipital regions, both with and without using drinking measures as covariates. Individually, however, the posterior central, parietal, and occipital areas showed significant reductions in ERP in the high-risk group. This reduction in ERP in the posterior centroparietal and occipital areas on analyzing individual leads is confirmed by the CSD analysis. Overall, using both ERP and CSD data, in comparing the high-risk group to the low-risk group, the right hemisphere as well as the more posterior centroparietal regions showed significant reductions in P300 amplitude (refer to electrode map, Fig. 1; CSD map, Fig. 5).

In attempting to understand the significance of this reduced amplitude, one needs to examine the possible significance of the P300 component itself. Early work established

the P300 as a brain potential evoked by cognitive processes, even in the absence of an exogenous stimulus.<sup>14-16</sup> The functional significance of this component of the ERP in cognitive processes may be evaluated by examining its potential sources, polarity, and variability with tasks.

One view that has been consistently expressed<sup>17-24</sup> is that the P300 represents cortical inhibition. Negative shifts in cortical potentials, such as those that occur during seizures, are regarded as reflecting excitation of cortical neural networks, whereas positive shifts seem to be inhibitory.<sup>22</sup>

Roberts et al.<sup>24</sup> implicate the reticular nucleus of the thalamus in differentially inhibiting those areas of the cortex that are not activated by a stimulus. This attractive theory could explain the widespread, yet differential, presence of the P300 wave.

Birbaumer et al.<sup>21</sup> conducted a series of experiments using a Go-No-Go paradigm, wherein the presence of stimulus 1 warned the subject of the possible occurrence of either stimulus 2, which required a button press (Go), or an irrelevant stimulus that did not require a button press (No-Go). P300 components evoked by the No-Go paradigm had larger amplitudes and were maximal over the contralateral (to the motor response) hemisphere, and in the frontal and central areas. The Go paradigm, in contrast, evoked P300 components that had asymmetrical, midsagittal, and parietal distribution. When the contingent negative

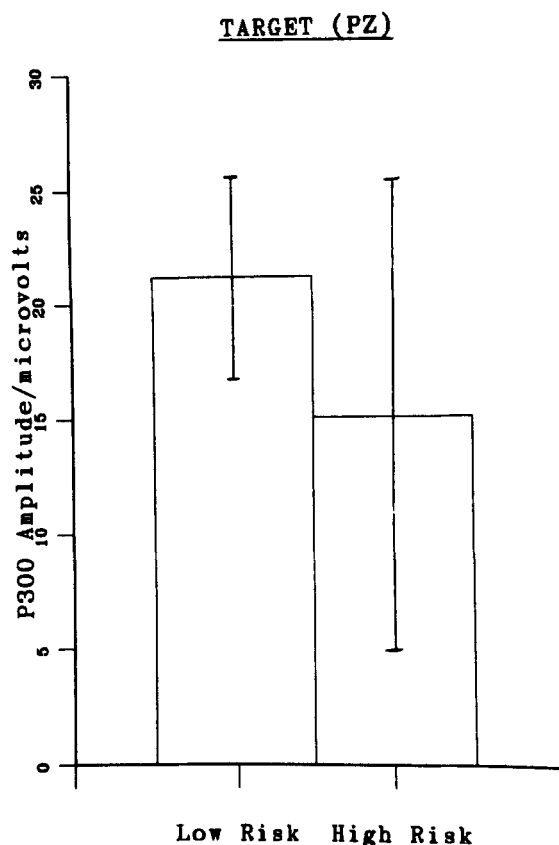


Fig. 4. Histogram of P300 amplitude at Pz (low-risk group versus high-risk group).

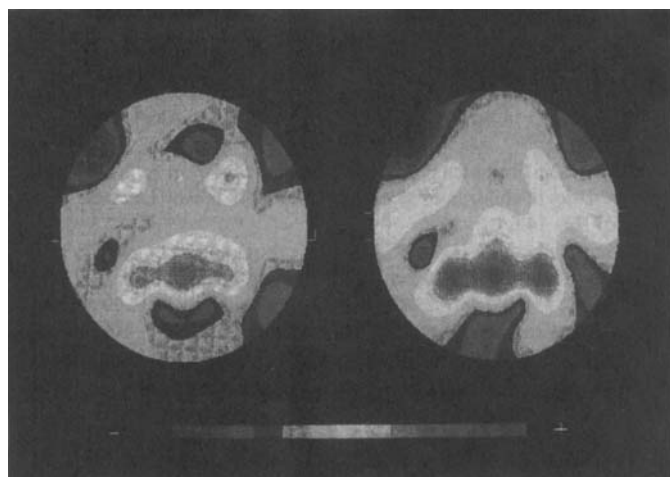


Fig. 5. CSD map of high-risk group (left) versus low-risk group (right).

variable was factored out of the waveform, the differences in P300 attributes between the paradigms still remained significant. Therefore, it seemed that active suppression of the motor response, which had been anticipated by the previous stimulus, manifested itself by an inhibitory, positive wave over the area of cortex responsible for that response.

This active inhibition of the cortex that was previously in a state of readiness is also dependent on variables, such as

surprise value that is frontally dominant or signal value with parietal dominance.<sup>25</sup> In oddball paradigms, for instance, the rarer the stimulus, the more the element of surprise involved; thus, the larger P300 amplitude is commonly largest in the centroparietal area, reflecting the signal properties in these experiments. In addition, the more deviant a target from the frequent stimuli, the easier it is to distinguish, making the P300 amplitude to the target stimulus larger in comparison with the nontargets. However, when the degree of difficulty of the task increases (i.e., as the characteristics of the nontarget approach those of the target), the ability to discriminate between the two becomes more demanding, and each nontarget needs to be more thoroughly evaluated for target attributes before being discarded. This theory lends itself to the suggestion that there would be smaller P300 amplitude differences between target and nontarget in more complex.<sup>3</sup> In these tasks, each nontarget is "part target" by virtue of its similarities to the target and therefore elicits a larger P300 wave than it would were it more dissimilar. Thus, an easier task would elicit larger P300 differences between target and nontarget responses. Although we did not examine levels of task difficulty, per se, the auditory oddball paradigm we used is a relatively simple task. Because this auditory oddball task involved an easy discrimination between target and nontarget stimuli, it elicited very large P300 waves in response to target stimuli in the low-risk individuals. Our study found a significant ERP reduction in high-risk males compared with low-risk males using this task in contrast to the conclusion of the meta-analysis by Polich et al.<sup>8</sup> that easy tasks would be less likely to elicit P300 differences between high-risk and low-risk subjects.

Inhibition of the relevant cortical areas apparently facilitates efficient processing of a given stimulus. The implication of this speculation is that the reduced P300 in the high-risk groups, compared with the low-risk groups, may indicate cortical disinhibition in the high-risk group and a reduced ability to probability match. What this means clinically is subject to speculation. One could postulate that it is this inherent physiological disinhibition of the cortex in the high-risk group that is associated with more of a tendency to impulsivity and a higher incidence of alcoholism in this group.

It has, in fact, been shown that the degree of reduction in P300 amplitude in a given population at risk for alcoholism is inversely correlated with the amount of future substance abuse. In an elegant study by Berman et al.,<sup>26</sup> visual ERPs were elicited from 36 boys with the mean age of 12 years. Four years later, the subjects filled out a questionnaire that was used to derive a contemporary substance abuse score. Those with the lowest P300 amplitude scores 4 years earlier now had the highest substance abuse scores (i.e., the reduction in P300 amplitude was a good predictor of future alcohol and substance abuse).

In our study, the variability in the amplitude of the P300 was more pronounced in the high-risk group (Fig. 4). This

is not surprising, considering that alcoholism is a genetically heterogeneous disease and the variability of the P300, a potential biological marker of this illness, reflects this heterogeneity in those at risk for developing the disease.

We speculate that in the current experiment, the subject generates a "template" to nontarget stimuli. When confronted, however, with the relevant target auditory oddball tone, the low-risk subjects may be said to act appropriately by sending the sensory impulses back to the thalamus to be processed in the relevant area (the pulvinar in this instance). From there, impulses are sent to the reticular nucleus that is inhibitory to all of the thalamic nuclei. This differential inhibition of the various thalamic nuclei would then propagate via thalamocortical pathways to the relevant cortical area (the parietal association cortex in this instance), as well as the entire cortex. This would manifest itself as a diffuse P300 waveform that would be maximal in the centroparietal area.

In the high-risk group, however, this circuit would in some way be defective, leading to less than optimal inhibition of the frontal and parietal association cortices and thus lead to defective stimulus processing. Although an interesting theory, which in addition explains the role of attention and motivation as a variable in P300 production (by implicating the limbic system via the dorsal nuclei and the frontal lobe via the anterior nuclei and the diffuse projection nuclei involved in alerting processes), this theory is still very much speculation. More work needs to be done in this area.

Better monitoring techniques and perhaps even intraxial electrode placement are possibilities. In an interesting experiment, Yingling and Hosobuchi<sup>27</sup> recorded the P300 from the thalamus in a chronic pain patient during auditory and visual oddball paradigms. A negative endogenous component of the same latency as the P300 was elicited even in the absence of an overt motor response. They concurred with Desmedt and Debecker<sup>28</sup> that the P300 "reflects transient inhibition of the reticulo-thalamo-cortical activating mechanisms under control of the prefrontal cortex after closure of the decision process in the target detection task."<sup>29</sup>

In their meta-analytic review of ERPs in males at risk for alcoholism, Polich et al.<sup>8</sup> note that, in normal subjects, the P300 amplitude increases in amplitude through adolescence, probably reflecting the maturation of the central nervous system during this period. If this maturational process is paralleled in the high-risk population, one would expect the P300 amplitude in this group also to increase during adolescence. Whether this in fact does take place or whether the high-risk population shows either a developmental lag or an arrest of brain maturation, as reflected by the P300 amplitude, has not been closely studied. Hill et al.<sup>6</sup> postulate from their ERP data on the children of alcoholics that these children may have a maturational lag. Thus, the lower P300s in the high-risk group may represent a maturational delay in this group.

We were concerned that the statistically significant difference in the alcohol consumption patterns of high-risk and low-risk males may have affected the outcome of our study. When the results were analyzed using number of drinks per day and per month as covariates, however, there continued to be statistically significant differences in P300 amplitude between the groups in the appropriate areas.

Using a simple auditory oddball task, we find statistically significant differences in the P300 amplitude between the high- and low-risk subjects. This demonstrates the reliability of the P300 amplitude in targeting populations at risk for alcoholism despite age, task difficulty, or sensory modality used to elicit the ERP. We therefore conclude that the P300 seems to be a reliable biological marker for alcoholism in both the auditory and visual paradigms in both children and young adult males at risk for the development of the disease.

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