Event-related brain potentials are different in individuals at high and low risk for developing alcoholism*

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ABSTRACT Event-related brain potentials (ERPs) from normal drinkers with and without a family history of alcoholism were compared. Three separate groups of 10 subjects each (5 with and 5 without a family history of alcoholism) ingested either a placebo or ethanol at 0.56 or 0.94 g/kg. In each comparison, ERP components elicited in conjunction with subjects’ decisions about task-relevant stimuli were significantly reduced in amplitude in individuals with a family history of alcoholism. Additionally, both the latency of the positive component and reaction times to correctly detected targets were significantly later in individuals with a positive history of alcoholism than in those without such a history. These group differences were apparent both with and without a challenge of alcohol. The data suggest that brain functions are different in individuals at high and low risk for the development of alcoholism (i.e., those with and without a family history of alcoholism, respectively).

The connection between family background and alcoholism is strong. Goodwin (1) and others (2) have estimated that individuals with alcoholic relatives are at least 4 times more likely to develop alcoholism than are adults in the general population.

Evidence that genetics partly determines this relationship has come from several types of studies. For example, the concordance of alcoholism in monozygotic twins is nearly double that in dizygotic twins (e.g., refs. 3 and 4). Similarly, studies of drinking in individuals separated at a young age from their biological parents find that alcoholism in the biological parents (but not the rearing parents) is predictive of drinking problems in the adoptees (e.g., refs. 5 and 6). These results and others led Dietrich and McLean (7) to conclude that “a large part of the variance in alcohol susceptibility is due to genetic differences.”

There is evidence that suggests brain function might be involved in the genetic predisposition to alcoholism. In rats, alcohol’s effects on neurophysiological functions are very different depending on the genetic strain of the rat (8). In humans, several studies have found a higher incidence of hyperactivity in the children of alcoholics (see ref. 9 for review), and an excess of high-frequency activity has been reported in the electroencephalogram (EEG) of the 12-year-old sons of alcoholic fathers (10). Thus, it is conceivable that the genetic influence on the development of alcoholism might be reflected in neurophysiological functions in humans.

Human brain function has been studied by EEG and by the use of computer-averaged event-related potentials (ERPs) associated with the processing of specific information. Several studies have shown that acute ingestion of alcohol markedly depresses the amplitudes of ERP components associated with sensory and cognitive processing (e.g., refs. 11–13). In one such study, Neville et al.** observed that alcohol had different effects on ERPs in individuals with a first-degree relative who was alcoholic (FH+ when compared to those without such a family history (FH-). However, since these subjects (Ss) were not matched for personal drinking habits, the results could not be attributed unambiguously to family history for alcoholism.

In the present study, we examined ERPs in a vigilance task before and after ingestion of placebo or alcohol to test further the hypothesis that central nervous system functions may be differentially affected by alcohol in FH- and FH+ individuals. We now report that differences in brain functions are apparent in FH- and FH+ individuals even without a challenge of alcohol.

METHODS

Subjects. Ss were classified as FH+ if their responses on a questionnaire (14) indicated that their biological father met the criteria for primary alcoholism (i.e., when drinking behavior interfered with his marriage or job, and when such problems occurred in the absence of other psychiatric or drug-related problems). Fifteen FH- Ss were matched with 15 FH+ Ss on personal drinking habits (range, 1–84 drinks per month), height/weight ratio (range, 0.39 to 0.52 inches/pounds), age (21–26 yr), sex (male) and socioeconomic class (university community). Neither Ss nor experimenters were aware of the family history classification until the study was completed. Ss reported to the experimental room at 0700 hours after fasting since 2300 hours the previous night.

The 15 pairs of Ss were divided into one of three dosage groups which received a placebo or ethanol at 0.56 or 0.94 g/kg of body weight. Although FH+/FH- S pairs within a dosage condition were closely matched, there were differences in the personal drinking habits across the dosage conditions. The group that received the higher dosage reported drinking an average of 36.6 SD ± 32.7 drinks per month whereas the placebo and low-dosage groups reported drinking on average 14 (SD ± 11.4) and 12.3 (SD ± 13.2) drinks per month, respectively.

Procedures. The alcohol given high-dosage Ss was mixed with 4 vol of sugar-free tonic water. Ss receiving the placebo drank a volume of tonic water equal to the amount they would have received as high-dosage Ss, and they drank it from cups whose rims had been wetted with alcohol. Both high-dosage and placebo Ss were given 24 min to drink and then they chewed

Abbreviations: Ss, subjects; ERPs, event-related potentials; FH+, family history positive; FH-, family history negative; EEG, electroencephalography or electroencephalogram; dB, decibel(s).

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gum for 6 min to clear the mouth of alcohol which might have affected breath analysis for blood alcohol concentration. The low-dosage Ss drank a 4:1 mixture of sugar-free soda water and alcohol in a 5-min period followed by 10 min of gum chewing. For all Ss, one "block" (21 min) of ERP recording preceded the drink period, a second followed immediately, and a third began one-half hour afterwards (data from two subsequent blocks will not be considered here). Breath samples for blood alcohol level were taken 30 min after Ss first began to drink and after both the second and third ERP recording periods.

In each ERP block, Ss listened to trains of six 300-msec tone bursts. In 20% of the trains, the sixth stimulus in the train was a 75-msec tone burst. The task for the Ss was to press a button within 1 sec of the offset of this short "target" tone burst. Because trains with short tone bursts in the final position occurred randomly and on average once every 39 sec, this task required rather sustained vigilance.

Stimuli. The tone bursts were either 540 or 1,000 Hz, with 5-msec linear rise-fall times. They were presented binaurally at 60-decibel (dB) sound pressure level (referenced to $2 \times 10^{-4}$ dynes/cm$^2$) via TDH-39 earphones. Use of a continuous background of white noise ensured that the tone bursts were approximately 25 dB above each S's threshold. Within each train, tone bursts began every 0.5 or every 1.0 sec; the time from the onset of the last (sixth) stimulus to the onset of the first stimulus in the next train was either 2 or 6 sec. The various combinations of stimulus frequency and interstimulus and intertrain intervals were counterbalanced or randomized within each ERP recording period. This report will only consider data for target and nontarget sixth stimuli (averaged without regard to the stimulus frequency or interstimulus or intertrain intervals).

Recording and Data Analysis. The EEG was recorded from Ag/AgCl electrodes over frontal, central, and parietal locations (Fz, Cz, and Pz; international 10-20 system) referenced to linked mastoids. Eye movements were recorded from an electrode placed below the canthus of the left eye and referenced to an electrode above the canthus of the right eye.

The EEG was amplified with a bandpass of 0.1-70 Hz and was recorded on an FM tape recorder for off-line analysis. The EEG was digitized every 4.7 msec for 200 msec prior to and 1,000 msec after stimulus onset. After rejection of trials contaminated by eye movements or amplifier blocking, ERPs associated with equivalent stimulus and response conditions were averaged.

Three types of measurements were made on the ERPs generated by the sixth stimuli in a train: (i) maximal (peak) voltage, (ii) peak latency from stimulus onset, and (iii) average voltage within a time window. Zero voltage was defined by the average of the 200-msec prestimulus baseline. Peak amplitude and latency were obtained for the positive peak between 290 and 555 msec and six average voltage measurements were made in 94-msec windows starting at 0, 100, 200, 300, 400, and 500 msec.

Statistical analyses of these measures were performed by using a 5 (Ss) by 3 (electrodes) by 3 (recording blocks) by 2 (family history classifications) by 3 (dosage groups) analysis of variance, with the S factor nested under both family history and dosage groups. Reaction time and percentage of correctly detected targets were tested with similar analyses but with electrode location omitted as a factor.

RESULTS

Blood Alcohol Concentration. The blood alcohol concentration estimates derived from breath samples peaked between the second and third recording blocks at 66.0 and 97.6 mg/100 ml for the low- and high-dosage groups, respectively. In agreement with previous work (14), however, blood alcohol concentration did not distinguish FH+ Ss from FH− Ss.

ERP Results. 1. Targets. ERPs from FH− and FH+ Ss to correctly detected targets before and after drinking for all three groups are shown in Fig. 1. The ERPs were characterized by two negative peaks—mean latencies, 119 and 263 msec—both largest frontally, and by a positive component largest from central and parietal sites that peaked on average at 441 msec. These three ERP components (referred to as N1, N2, and P3) are typical of what other investigators report to correctly detected targets.

Comparison of ERPs from FH+ and FH− Ss reveals that P3 was markedly suppressed in blocks 2 and 3 for FH+ Ss but was comparatively unchanged for FH− Ss. The family history difference was evident after ingestion of both doses of alcohol and after ingestion of placebo (Table 1). Statistical analyses of the mean voltage between 300 and 400 msec revealed that P3 amplitude was significantly smaller in FH+ Ss for all three dosage groups ($P < 0.015$). Moreover, combining the data across dosage groups revealed that both the peak amplitude and average voltage measure displayed a significant block $\times$ family history interaction ($F(2,48) = 4.1, 9.5, P < 0.023, P < 0.001$, respectively). Alcohol reduced P3 amplitude (average voltage measure) in both FH− and FH+ Ss [block $\times$ dose interaction $F(4,48) = 2.59, P = 0.048$]. Nonetheless the suppression of P3 in FH+...
relative to FH− Ss was maintained under all dosage conditions. The mean percentage reduction of P3 from block 1 to blocks 2 and 3 is shown in Fig. 2 to correct for the fact that FH+ high-dosage Ss had very small P3 amplitudes in block 1 (Table 1).

The increase in latency of P3 from block 1 to blocks 2 and 3 was significantly greater in the FH+ than in the FH− Ss. When averaged across electrode location and dosage groups, the peak latency increased about 75 msec for FH+ Ss but only about 30 msec for FH− Ss (block × family history interaction F = 4.64; P = 0.014) (Table 2).

2. Nontarget sixth stimuli. After nontarget sixth stimuli, a slow positive component occurred in all groups (Fig. 3). At latencies exceeding 200 msec, ERPs for FH+ Ss were consistently about 2 μV less positive at the parietal location (Pz) than ERPs from the FH− Ss. This difference was apparent in block 1 (i.e., prior to ingestion) as well as in blocks 2 and 3. The electrode location by family history interaction was significant for each of the average voltage measurements beginning at 200, 300, 400, and 500 msec [F(2,48) = 4.45, 9.28, 13.57, and 17.39; P < 0.028, 0.009, 0.008, and 0.006, respectively]. Moreover, the average voltage measured between 300 and 400 msec also displayed a significant block × family history interaction, indicating that, for this stimulus as well as for target hits, the average voltage dropped more across blocks for FH+ than for FH− Ss [F(2,48) = 14.6; P < 0.039].

Behavioral Results. FH+ Ss tended to be less accurate (95%) in responding to the targets than were FH− Ss (97%) [F(2,48) = 2.1; P = 0.15] and their reaction times increased significantly more across blocks than the reaction times of FH− Ss [block × family history F(2,48) = 3.3; P < 0.045] (Table 3).

DISCUSSION

In three separate comparisons of normal drinkers, the brain responses of Ss at high risk for the development of alcoholism

![Graph](https://example.com/graph.png)

**Fig. 2.** Percentage of P3 amplitude relative to block 1 (calculated from Table 1).

### Table 1. Mean amplitudes (μV) between 300 and 400 msec for ERPs to correctly detected targets

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<tr>
<th></th>
<th>Placebo</th>
<th>Low dosage</th>
<th>High dosage</th>
<th>Mean</th>
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<tr>
<td>FH− Ss</td>
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<tr>
<td>Block 1</td>
<td>7.98</td>
<td>9.12</td>
<td>8.11</td>
<td>8.39</td>
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<tr>
<td>Block 2</td>
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<td>6.75</td>
<td>4.41</td>
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<tr>
<td>Block 3</td>
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<td>6.91</td>
<td>4.45</td>
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<td>FH+ Ss</td>
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<table>
<thead>
<tr>
<th>Family history positive</th>
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<tr>
<td>Block 1</td>
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(FH+) were different from the responses of those at low risk (FH−). FH+ Ss displayed reduced amplitudes of ERP components associated with the decision that a stimulus was or was not a target when compared to ERPs from FH− Ss.

The late positive component (P3) elicited when FH+ Ss correctly detected targets was markedly reduced after the first recording block, regardless of whether Ss ingested placebo or alcohol. The observed group differences were statistically significant according to both area and peak measures of amplitude. The peak latency of P3 was also significantly delayed in FH+ compared to FH− Ss. Although this latency increase probably contributed to the reduction in the average amplitude between 300 and 400 msec, it should not have contributed to the reduction in the peak amplitude measure.

Ethanol reduced the amplitude of P3 (relative to the before-drink base line) in both FH+ and FH− groups. Two factors potentially confounded this effect of ethanol—the drinking protocol for low-dosage Ss differed slightly from that used for the other groups, and the high-dosage group reported higher ethanol intake in their personal drinking habits. Nevertheless, the suppression of P3 amplitude with increased ethanol intake is consistent with other studies (10–12).

![Graph](https://example.com/graph2.png)

**Fig. 3.** ERPs, recorded from parietal location (P2), to the nontarget events at the end of the stimulus trains. ERPs are averaged over the three dosage groups (i.e., 15 g/kg with FH+; 15 g/kg with FH−). Note that the FH+ waveform is less positive than the FH− waveform in all three blocks.
It is important to note that the differences in drinking habits and drinking protocols mentioned above could not have contributed to the greater suppression of P3 amplitude in FH+ Ss because both drinking protocol and personal drinking habits were equivalent for FH+ and FH− Ss within dosage groups. Indeed, the fact that the group differences were apparent and statistically significant in each of the different dosage comparisons suggests that the relationship between family history for alcoholism and P3 amplitude is robust.

The slow positive wave elicited when Ss decided that the last event in the stimulus train was not a target also was significantly reduced in amplitude in FH+ compared to FH− Ss. A poorly synchronized P3 component may have contributed to this group difference because the 300- to 400-msec average voltage decreased more for FH+ Ss than FH− Ss in blocks 2 and 3, as it did for targets. By contrast with the ERPs to targets, however, group differences in ERPs to these nontargets were already evident at the beginning of the recording session. Moreover, this group ERP difference occurred by 200 msec (i.e., before P3 onset), suggesting that ERP components in addition to P3 may be different in FH+ Ss.

Because two additional investigations have found reduced decision-related P3 components in FH+ Ss [Neville et al. (1980); H. Begleiter, B. Porjesz, B. Bihari, and B. Kisin (personal communication) who compared 8- to 13-year-old sons of alcoholic and nonalcoholic fathers], the particular details of experimental procedure do not appear to be critical in revealing differences in P3 between FH− and FH+ individuals. The Begleiter et al. results, obtained in a nonalcoholic protocol, together with the present results showing group differences in pre-ingestion ERPs and after placebo, indicate that alcohol is not required to observe differences in brain function between FH+ and FH− Ss.

The functional significance of reduced decision-related ERP components in FH+ Ss can be interpreted in the light of a large literature (e.g., ref. 15). The amplitude of P3 has consistently been related to the cognitive evaluation of stimulus events rather than to the physical parameters of stimulation. When attentional resources are reduced or directed away from the evoking stimulus, P3 amplitude is reduced (e.g., ref. 16). Moreover it has been shown that the latency of P3 is determined by the time it takes to identify and to classify a stimulus (17, 18). Thus, the reduced amplitude and increased latency of P3 in the FH+ Ss suggest that they either could not or would not devote as many resources to the task. This interpretation is consistent with the behavioral data indicating that FH+ Ss were slower and less accurate in identifying the targets.

Further studies are required to clarify the difference in brain responses between FH+ and FH− Ss. P3 occurs in many guises (19) and knowledge of how this component is affected in different situations should help to specify the processes that underlie FH+/FH− difference. It will also be important to determine the neural mechanisms that generate ERP components that are different in individuals at high and low risk for developing alcoholism. Although the neural origins of cognitively labile ERP components are not well understood, new methods and models are becoming available to solve this problem (e.g., refs. 20 and 21). Recently, Halgren et al. (1980) and McCarthy et al. (1982) recorded P3 simultaneously from scalp electrodes and from depth electrodes within the human brain, and their data suggest that the hippocampus may be an important contributor to P3 potentials. Several models of P3 in experimental animals are under development and these will help to clarify the cellular and biochemical processes that generate this potential. Finally, it will be important to determine whether the mechanisms underlying the reduced amplitude and increased latency of P3 contribute to the increased risk of developing alcoholism in FH+ Ss or whether the altered ERPs are only correlated with increased risk. In either case, ERPs may help to identify individuals at risk and thus may help to clarify the mechanisms that underlie increased susceptibility to alcohol dependence.

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