
Neurophysiological Factors in Individuals at Risk for Alcoholism

Bernice Porjesz and Henri Begleiter

Abstract. The literature dealing with electrophysiological research in individuals at risk for alcoholism is reviewed. Event-related potential (ERP) and electroencephalographic (EEG) differences between family-history-positive (FHP) and family-history-negative (FHN) men have been reported both prior to the ingestion of alcohol and following alcohol challenge doses. At present, the most robust of these electrophysiological findings is the lower P3 amplitude of the ERP, which has now been replicated in several laboratories. This perhaps provides a phenotypic marker, distinguishing those at risk for alcoholism. However, its specificity for alcoholism and the role of gene-environment interactions in the development of alcoholism remain to be determined.

1. Introduction and Background

Over the last few decades, electrophysiological aberrations in alcoholics have been extensively investigated with the use of electroencephalographic (EEG) and event-related potentials (ERP) (for reviews see¹⁻³). Some of the salient findings are as follows: Abstinent alcoholics have low EEG alpha production and produce an excessive amount of fast-frequency activity.^{1,4,5} The auditory brainstem potential (BSP) is delayed in alcoholics.⁶⁻¹⁰ Alcoholics manifest low-amplitude P3 components of the ERP to target stimuli.^{11,12} It has been found that with prolonged abstinence from alcohol, some of these electrophysiological aberrations recover (e.g., BSP) while others (e.g., P3) do not.³

For many years, these brain aberrations were attributed to the neurotoxic effects of prolonged chronic alcohol exposure on the brain, nutritional deficits,

or an interaction of alcohol and nutritional-related factors. More recently, the evidence is amassing that some of these electrophysiological aberrations may antecede the development of alcoholism and may involve a genetic predisposition to alcoholism.

There is increasing evidence from population genetics studies that certain individuals are at risk for developing alcoholism. Specifically at higher risk seem to be sons of alcoholic fathers, who are four times more likely to develop alcoholism than sons of nonalcoholics^{13,14} even when they are separated from their biological parents soon after birth. Studies of male adoptees indicate that the biological rather than the adoptive parent is predictive of later drinking problems.¹⁴⁻¹⁹ Furthermore, the concordance rate for alcohol abuse between identical twins is almost double the rate for fraternal twins,²⁰ and patterns of alcohol consumption have been reported to be highly concordant among identical twins.²¹⁻²³ Taken together, these population genetic studies suggest that genetic factors may be involved, predisposing sons of alcoholics to alcoholism.

The identification of suitable biological marker(s) that are genetically transmitted would provide more definitive evidence that the etiology of alcoholism involves genetic factors. In addition, it could perhaps elucidate the potential nature of these genetic factors.

There is evidence indicating that both EEG and ERP characteristics are genetically determined. The production of fast EEG activity has been demonstrated to be genetically transmitted.²⁴⁻²⁶ In various studies, Vogel^{24,27} and his colleagues have reported on the hereditary nature of several EEG variants (monomorphic alpha, low-voltage EEG, EEG with alpha and beta diffusely mixed, EEG with frontoprecentral beta). These investigators maintain that the low-voltage and regular alpha EEG are inherited via an autosomal dominant mode, while the poor alpha or diffuse beta variants are under polygenic control.²⁴ Monozygotic twins manifest evoked potential (EP) waveforms that are as concordant with each other as EPs obtained from the same individual tested twice.²⁸ The P3 component of the ERP is more similar in identical twins than controls.²⁹

It is likely that brain function is involved in the genetic predisposition to alcoholism and it is possible that electrophysiological events may serve as biological markers. Therefore, investigating these electrophysiological, genetically determined measures of brain function provides an important approach to the study of possible genetic factors in alcoholism.

2. Electroencephalography

For the last several decades a number of investigators have observed that resting-state EEG activity recorded from awake abstinent male alcoholics manifests an overabundance of high-frequency activity (beta, fast EEG) and a deficiency in lower-frequency EEG activity (e.g., alpha) (for review see Begleiter and Platz¹). As mentioned previously, the production of fast EEG activity has been demonstrated to be genetically transmitted.²⁴⁻²⁶

These EEG findings in alcoholics, coupled with the population genetic studies of alcoholism, suggest that subjects at risk for alcoholism (male offspring of male alcoholics) would manifest an excess of fast EEG activity. Gabrielli *et al.*³⁰ tested this hypothesis in a sample of 27 Danish children of alcoholics compared with children of nonalcoholics. As hypothesized, they observed that male (but not female) offspring of alcoholics manifested fast EEG activity compared to controls.

A number of studies have investigated the EEG responses to alcohol in high- and low-risk subjects. In one study, Pollock *et al.*³¹ report that high-risk sons (HR) of alcoholics (19–21 years old) exhibit greater increases in slow alpha activity (7.42–9.46 Hz) and greater decreases in fast alpha activity (9.75–12.10 Hz) after a 0.5 g/kg dose of alcohol compared to low-risk (LR) subjects. The increases in slow alpha activity were observed at 30 and 120 min postethanol while the decreases in fast alpha were observed only at 120 min. In addition, HR subjects manifested greater decreases in alpha frequency 30, 60, and 120 min after alcohol administration than did controls.

The investigators do not report any EEG differences between HR and LR groups prior to ethanol ingestion and limit their analyses to theta and fast and slow alpha activity. This is puzzling in light of the earlier results from their own group by Gabrielli *et al.*³⁰ of excessive beta activity in sons of alcoholic fathers without the ingestion of alcohol. In another paper, Pollock *et al.*³² report they do not replicate Gabrielli's findings. While the HR subjects did not report a higher amount of alcohol consumption than LR subjects, they reported needing significantly more drinks to "feel tipsy." Taken together, these results suggest that HR subjects while being more sensitive to the physiological effects of alcohol, are subjectively less sensitive to its effects.

In another laboratory, Ehlers and Schuckit (1990) reported that males with family histories of alcoholism have more power in the fast-frequency alpha range (9–12 Hz) than males without family histories of alcoholism.³³ Family-history-positive (FHP) males responded less intensely to an ethanol challenge than family-history-negative (FHN) males in terms of their fast frequency of alpha. Furthermore, FHP men manifested more beta activity 90 min postethanol than did FHN men. "Moderate" drinkers were found to have more energy in the beta frequency range than the "low" drinkers in the FHN group; interestingly, while FHP subjects had more beta energy than FHN subjects, no differences between "low" and "moderate" drinkers' beta activity were found in the FHP group.

Thus, the EEG findings of these two laboratories do not agree in terms of the fast alpha activity, the frequency band they investigated in common. While Ehlers *et al.*³⁴ report *less* physiological responsiveness and "sensitivity" to ethanol in the FHP compared to the FHN group, Pollock *et al.*³¹ report *more* responsiveness and more sensitivity. Yet both groups agree that high-risk men report feeling less intoxicated after a single dose of alcohol.^{31,35,36}

In another interesting study, Pollock *et al.*³⁷ address the issue of physiological and subjective sensitivity. These investigators attempt to test two hypotheses, namely:

1. HR subjects will manifest greater physiological change and less subjective sensitivity to alcohol compared to controls.³⁸ Tarter *et al.*³⁸ speculate that prealcoholics are particularly vulnerable to the effects of alcohol; they exhibit a great deal of physiological lability and alcohol may regulate their physiological functioning. They have difficulty identifying their subjective states because of this physiological lability.
2. HR subjects will manifest less physiological and subjective sensitivity to alcohol.³⁹ Goodwin³⁹ speculates that in order to develop alcoholism, individuals possess high initial tolerance for alcohol effects (defined as individual variation in sensitivity to alcohol, not acquired tolerance associated with development of dependence).

To test these hypotheses, Pollock *et al.*³⁷ divided a sample of FHP males into those exhibiting the most EEG change (mean alpha frequency) following ethanol administration and those exhibiting the least EEG change (similar to controls). In terms of their subjective intoxication ratings, they found that the two groups differed in terms of their time course. The group manifesting the most EEG change differed from controls at 55 but not 25 min postethanol, while the group manifesting the least EEG change differed from controls at 25 but not 55 minutes postingestion. The group with the least EEG change did not report higher levels of intoxication at 25 than 55 min postethanol, while both the controls and subjects with the greatest EEG changes did.

The characteristics of the groups manifesting the greatest EEG change can be related to Tarter's hypothesis, while those manifesting the least change can be related to Goodwin's hypothesis. However, Tarter's hypothesis about physiological lability was not adequately addressed in this study, as no placebo data and measures of within-subject variability of mean alpha frequency were obtained.

It is important to ascertain whether there are EEG differences between HR and LR groups prior to alcohol ingestion, as differential responses to ethanol challenge have been reported in individuals depending on their preethanol resting EEG signature.⁴⁰ Subjects manifesting poor alpha activity prior to ethanol manifested the most synchronization following alcohol, whereas those with regular preethanol alpha exhibited a slight change. Thus the effect of alcohol on EEG depends on prealcohol EEG pattern, which is under genetic control. Propping maintains that EEG with poor alpha or beta reflects a stronger ascending reticular activating system. As mentioned previously, Vogel²⁴ has identified different genetic EEG patterns. He postulates that low-voltage and regular alpha are autosomal-dominant, while poor alpha and diffuse beta are under polygenetic control.

On the basis of Propping's⁴⁰ work, it seems that subjects with poor alpha or beta in their prealcohol EEG would be more susceptible to ethanol effects. Therefore, it would be important to know if in Pollock's study the HR sample consisted of more subjects manifesting more beta activity and poor alpha than the LR group—perhaps explaining their greater response to alcohol.

In addition, it would be important to characterize the EEG in the control groups before alcohol, as they may consist of individuals with different EEG variants as well. It is possible that the lack of agreement between EEG laboratories is a function of differences in the composition of their control and HR groups in terms of EEG patterns.

As alcoholics have been reported to have poorly synchronized EEG, it can be postulated that their offspring would be more likely to inherit this pattern. However, Propping *et al.*⁴¹ found that female and not male alcoholics manifested this pattern, as did their relatives.

If both groups are considered together, it seems that alcoholism is not a homogeneous disease. Perhaps the alcoholics with desynchronous resting EEG (men and some women) represent a group who use alcohol to relax and synchronize their alpha activity (Cloninger's Type 1).⁴² Alcohol normalizes their physiological function. These alcoholics probably correspond to Pollock's HR group who respond more to alcohol and are most likely more labile, supporting Tarter's hypothesis. Alcoholics with synchronous EEG probably correspond to Pollock's HR group who do not respond to alcohol as well as to Ehler's group as a whole, showing less responsiveness. However, until studies are performed in which EEG patterns are characterized before and after ethanol and placebo challenges, these conclusions remain speculative.

3. Event-Related Potentials

The event-related-potential (ERP) techniques offer a unique approach for assessing level of brain functioning, as they permit simultaneous observation of electrophysiology and cognition. An ERP is obtained by recording the time-locked brain electrical activity following the delivery of a discrete stimulus to any sensory modality (e.g., auditory, visual) with noninvasive scalp electrodes. Signal-averaging techniques make it possible to extract these time-locked neuroelectric signals (ERPs) from the background random "noise," which cancels out with these procedures. Depending on stimulation properties, task requirements, and recording sites, these time-locked signals represent activity at neural generators from the peripheral end-organ to higher integrative centers to output areas of the brain. The quantitative measurement of salient features extracted from ERP recordings provides objective evaluation of neural processes involved in sensory reception, cognitive and integrative functions, and output. Thus, with the use of these sophisticated neurophysiological techniques, the functional integrity of various neuroanatomical systems of the brain (from peripheral end-organ to neocortex) can be assessed.

In addition to being sensitive to sensory aspects of information processing, ERP techniques have proven to be useful in indexing electrophysiological concomitants of complex cognitive tasks.⁴³⁻⁴⁵ They can be recorded in conjunction with behavior, or even when no behavioral response is required; they can be

recorded to attended and unattended stimuli. As the ERP is sensitive to genetic,²⁹ sensory, cognitive, and motor aspects of information processing, it can be a valuable tool in studying the genetics of alcoholism.

For the past decade, in our laboratory we studied ERPs in subjects at risk for alcoholism.^{46,48,60} Begleiter *et al.*⁴⁶ studied HR boys between the ages of 7 and 13 who had no prior experience with alcohol. In each case, the father had received the exclusive diagnosis of alcoholism (DSM-III) and had been in treatment for alcoholism at some time. Boys whose mothers had ingested alcohol during pregnancy or who drank excessively after birth were excluded. Only boys without medical problems and without exposure to alcohol or other substances of abuse were included in this study. The LR group consisted of healthy normal boys matched to the HR subjects for age and socioeconomic status. They were included if they had no prior exposure to alcohol or other substances of abuse and had no history of alcoholism or other psychiatric disorder in first- or second-degree relatives. The same exclusion criteria were used in both the LR and HR groups.

A complex visual P3 head-orientation paradigm was used, as follows. The target stimulus was a rarely occurring aerial view of the head with the nose and one ear drawn in, rotated in four possible positions: nose up and right ear, nose up and left ear, nose down and right ear, nose down and left ear. Subjects pressed one of two microswitches indicating whether the right or left ear was presented, as quickly and accurately as possible. In the "easy" condition, the head was facing forward (nose up on screen) and the left or right ear appeared on the same side corresponding to the appropriate button; in the "difficult" condition, the head was facing back (nose down on screen) and the left or right ear appeared on the side opposite the corresponding button.

P3 amplitudes were found to be significantly smaller in the HR compared to the LR groups to all target stimuli. This group difference was most significant at the parietal electrode (where P3 is maximum) for the difficult condition. Principal component analysis with varimax rotation (PCAV) was also performed on the data. The results indicated that only the factor representing the P3 component was significantly different between the HR and LR groups.

This study was the first in the field to indicate a significant P3 difference between boys at high and low risk for alcoholism without exposure to alcohol. Since this original study, several laboratories including our own have replicated these findings, namely, O'Connor at the University of Connecticut, Whipple at UCLA, and Steinhauer at the University of Pittsburgh. O'Connor *et al.*⁴⁷ replicated the findings of reduced P3 amplitudes using the identical paradigm as Begleiter *et al.*⁴⁶ in an older group of HR males without the administration of alcohol.

In order to determine whether the P3 reductions in HR subjects was modality or task specific, Begleiter *et al.*⁴⁸ studied another group of HR sons of alcoholics. This was an auditory task (a modified auditory oddball) in which subjects pressed a button to rarely occurring tones presented at a random rate; accuracy was stressed over speed. Twenty-three matched pairs of FHP and FHN

males between the ages of 7 and 16 were studied; they were carefully interviewed to ascertain that they had no exposure to alcohol or illicit drugs.

The fathers in this sample of HR boys met the criteria for male-limited (Type 2) alcoholism.⁴² They manifested early-onset alcoholism with a high rate of recidivism requiring extensive treatment, often accompanied by petty criminality. Furthermore, the HR boys came from families in which alcoholism was highly heritable and was limited to males.

The results of this study indicated that the FHP boys manifested reduced P3 amplitudes. The reduction of P3 amplitudes in HR males with this auditory task suggests that the P3 voltage reductions are not modality or task specific; they seem to be present in auditory and visual paradigms under speed and accuracy conditions.

In another laboratory, Whipple *et al.*⁴⁹ examined ERPs in prepubescent boys at high risk for alcoholism with a more unusual paradigm. The paradigm was a complex visual continuous performance test (CPT) where stimuli changed along three dimensions: shape, color, and identity of a numeral; the subject silently counted each time a stimulus was identical to the one preceding it on all three dimensions. In agreement with Begleiter *et al.*^{46,48} and O'Connor *et al.*,^{47,50} Whipple *et al.*⁴⁹ report a reduction in the amplitude of the late positive complex (LPC), a P3-like component.

Despite the general consensus that P3 amplitudes are of lower voltage in HR males, some studies have failed to replicate these findings. Significant P3 amplitude reductions in sons of alcoholics have not been observed by Polich and Bloom^{51,52} and Baribeau *et al.*⁵³

Baribeau *et al.*⁵³ examined HR and LR subjects who were further subdivided according to the amount of alcohol they consumed (heavy versus light drinkers). An auditory selective attention paradigm⁴³ was used in which signals (500-Hz tones) were interspersed among standards (600-Hz tones) 10% of the time at a random ISI 630–880 msec; they were presented to the right and left ear randomly. Subjects were instructed to count the signals in one ear and ignore the other ear.

Although HR subjects did not exhibit reduced P3 amplitudes, the light drinkers manifested insignificantly smaller P3 in the inattention condition. HR subjects manifested significantly larger N100 components than LR subjects in the attention condition; this perhaps indicates that the HR subjects paid more attention than the LR subjects to the stimuli.

These results suggest that when attention is mobilized, P3 deficits are not apparent in the attended channel. Perhaps the lower P3 amplitude in the unattended channel would reach significance with a larger number of subjects. Furthermore, it is possible that the HR subjects find the tone discrimination task more difficult than the LR group (500 Hz versus 600 Hz) and hence needed to pay more attention. Finally, it seems that the subject sample represents an older group of HR individuals. There is a rather large age range (19–35), with mean ages of 27 (high risk—heavy drinking), 22 (high risk—light drinking), 24 (low risk—heavy drinking), and 25 (low risk—light drinking). It seems that these HR subjects may have already passed the age of risk. The sample perhaps is not

representative of a group at high risk for alcoholism, considering that those who already manifested alcoholic problems were excluded. If by this age they have not developed alcohol-related problems or become alcoholic, it is unlikely that they will; this represents a skewed sample of HR subjects, perhaps endowed with protective mechanisms. Certainly, their larger N100 component suggests they are atypical. Increased cognitive efficiency in nonaffected siblings of alcoholics has been reported by Hill *et al.*⁵⁴ in a P3 study. These investigators report an earlier P3 latency in these individuals. They suggest that this offers protection against the development of alcoholism in these nonaffected siblings.

Conflicting ERP results have been reported in various studies within the same laboratories at the University of California at San Diego examining college students with positive family histories of alcoholism. This is mostly the work of Neville^{55–57} and Polich.^{51,52,58,59}

Differences in P3 characteristics between subjects at high and low risk for alcoholism have been reported following the administration of either alcohol or a placebo. Elmasian *et al.*⁵⁵ studied the P3 and slow-wave components of the ERP in HR and LR male college students (aged 20–25) under placebo, low doses, and high doses of alcohol. Unfortunately, a different set of subjects was used for each dose, with only five pairs of subjects per group.

Elmasian *et al.* reported a significant P3 amplitude decrease in the HR compared to the LR subjects after alcohol or placebo administration. Elmasian *et al.*⁵⁵ explained their results in terms of expectancy for alcohol characterized by unusual brain events. The investigators also suggested that the results may be due to higher than normal alcohol intake in the mothers of the HR subjects.

In a subsequent study in the same laboratory⁵⁶ the LPC of the ERP in HR individuals was investigated without the ingestion of any liquid. This study eliminated expectancy effects, and in addition, mothers of all subjects were interviewed with respect to their alcohol and drug use. Group differences in the LPC were still observed between groups.

In yet another study, Schmidt and Neville⁵⁷ investigated ERPs in HR men while they were engaged in a visual language task. They found that the N430 component (a component related to semantic processing) was significantly smaller in men at high risk for alcoholism than in men at low risk. Moreover, the latency of N430 was directly related to the amount of alcohol consumed per occasion in the HR group. These results imply that neuronal function associated with language processes is affected by family history of alcoholism, and that there is an interaction between family history and alcohol consumed per occasion.

Polich and Bloom^{51,52} did not find P3 amplitude differences between male college students with and without family histories of alcoholism. Polich and Bloom⁵¹ reported an inverse correlation between the amount of alcohol consumption (drinks/sitting) and the amplitude of P3 in FHP subjects for a difficult intensity discrimination task only. Although there was a trend in this direction in FHN subjects, it was not significant. These results were obtained without the administration of alcohol. The authors concluded that FHP subjects are more sensitive to the effects of alcohol than are FHN subjects. While this is an

intriguing finding, it does not appear to be robust. When a similar intensity discrimination study was performed in the visual modality, no correlation between P3 characteristics and amount of alcohol typically consumed was found.⁵⁹ Furthermore, in another study designed to replicate Elmasian *et al.*,⁵⁵ Polich and Bloom⁵² not only did not replicate their previous findings of a placebo effect in the FHP group, but also now reported a correlation between P3 latency and amount of alcohol consumption in both FHP and FHN subjects. Thus, in the same laboratory, using samples drawn from the same basic population of students, their findings are not readily replicable. Previous alcohol consumption has been found to correlate with P3 amplitude only, particularly in FHP subjects,⁵¹ to correlate with P3 latency only,⁵² and not to correlate with any previous drinking variables.⁵⁹ In addition, N430 latency has been reported to correlate with number of drinks per occasion in HR subjects.⁵⁷ Furthermore, the initial placebo effect in FHP subjects⁵⁵ was not replicated in the same laboratory.⁵²

Taken together, the ERP results of the San Diego group may be spurious as they involve very small sample sizes. One possible explanation of lack of results in these laboratories is the mode of assessment of alcoholism in the fathers and families in general. A questionnaire is filled out by the son about his father's alcohol history. Very loose alcoholism criteria are employed and no verification of family history by collaterals is used. Thus it is possible that in a large percentage of subjects, the offspring are not offspring of alcoholics but of heavy or moderate drinkers. Therefore, it is conceivable that there is more agreement in the literature than had been heretofore suspected.

While it has been hypothesized that discrepancies in results between laboratories may be due to task difficulty, recent evidence fails to support this contention. O'Connor *et al.*,⁵⁰ using two different tasks that varied in terms of task difficulty, obtained identical results with both paradigms. Begleiter *et al.* replicated their finding of a lower P3 amplitude in HR subjects without the ingestion of alcohol in three different paradigms thus far, namely, using a complex visual response-compatibility/incompatibility design,⁴⁶ an auditory modified oddball paradigm,⁴⁸ and a visual discrimination paradigm.⁶⁰

The relationship between P3 characteristics and drinking history is as yet unresolved. Polich and Bloom⁵¹ have reported a relationship between drinking history and P3 amplitude in FHP but not FHN subjects for a difficult intensity discrimination task only. However, this relationship did not hold up in a similar intensity discrimination task in the visual modality where no relationship between P3 characteristics and amount of alcohol consumed was found.⁵⁹ Similarly, O'Connor *et al.*⁴⁷ report no relationship between any P3 characteristic and drinking history. However, in yet another study, Polich and Bloom⁵² report a correlation between P3 latency and amount of alcohol consumption in both FHP and FHN subjects. Steinhauer *et al.*⁶¹ also report a correlation between drinking history and P3 latency.

More recently, we investigated the effects of alcohol on cognitive ERPs in FHP and FHN subjects.⁶² Twenty-four pairs of male FHP and FHN subjects (aged 19–24) received a placebo and two ethanol doses (0.5 ml/kg and 0.8 ml/kg) mixed with 4 parts ginger ale on three separate occasions. A visual ERP para-

digm involving easy and difficult line orientation discriminations was utilized. ERPs and levels of intoxication (SHAS) were obtained preethanol and at 20, 60, 90, and 130 min following ethanol ingestion. Blood Alcohol Levels (BALs) were monitored at 10-min intervals throughout the test session.

The results indicate that the amplitude of P3 was significantly lower in FHP compared to FHN subjects prior to the administration of alcohol.⁶⁰ This replicates our previous findings of lower P3s in younger (6–12 year old) sons of alcoholics in an older sample and those of O'Connor and Whipple. The largest difference in P3 amplitude between groups occurred to the easy target to which FHN subjects manifested high voltages. These results are similar to those we previously observed in alcoholics with the same paradigm where the easy target elicited the greatest significant difference in P3 amplitude between groups.¹² This P3 amplitude difference was greatest at Pz and Cz electrodes.

The latency of P3 occurred significantly later to the difficult-discrimination target than to the easy target in both groups of subjects. Alcohol significantly increased the latency of P3 to the difficult target in both groups of subjects. This effect was maximal between 60 and 90 min postethanol and was significant at all electrodes except occipital.

The N1 amplitude was significantly decreased by alcohol ingestion, particularly for the nontarget stimulus at occipital leads. This result was more pronounced in the FHN than the FHP group. While N1 amplitude to nontargets remained depressed in amplitude in the FHN group throughout the test session, it recovered in amplitude by 90 min in the FHP group. These results suggest that the HR subjects exhibited more "tolerance" to alcohol than the LR group.

The N1 amplitude was not decreased to the difficult target and was somewhat decreased to the easy target by alcohol. These results support the finding by Roth *et al.*⁶³ that attentional factors can counteract the N1 decreases caused by alcohol, and Campbell and Lowick's⁶⁴ finding that the largest alcohol effects are obtained when attention is mobilized least (to nontargets). It was concluded that ERPs provide sensitive indices of state and trait variables involved in alcohol consumption and that different ERP characteristics are sensitive to different aspects of this multifaceted problem.

4. Summary and Conclusions

The foregoing review of the electrophysiological research in individuals at high risk for alcoholism indicates that they can be characterized by a low P3 amplitude of the ERP. This finding appears to be robust as it has been replicated in many different laboratories. The low P3 amplitude is apparent in HR subjects without exposure to alcohol. Reduced P3 voltages have been reported in abstinent alcoholics and have not been found to recover with prolonged abstinence.

There is substantial evidence indicating that electrophysiological characteristics (both EEG and ERP) are under genetic control. The P3 component has been reported to be more similar among MZ twins than controls.

Thus, the reduced P3 voltage in HR subjects perhaps provides a phenotypic marker for alcoholism. However, it remains to be determined whether those HR individuals manifesting low P3 voltages are in fact those who go on to develop the disease of alcoholism.

While it has been reported that HR subjects are also characterized by excessive high-frequency EEG without the administration of alcohol, this has only been reported in one laboratory and has not been replicated even within the same laboratory.

In addition to electrophysiological measures that differentiate HR from LR individuals without exposure to alcohol, other measures have been reported to differentiate individuals at risk with the use of alcohol challenges (changes in alpha, changes in N1 amplitude of the ERP). While these electrophysiological measures could represent vulnerability markers for alcoholism, there has not been sufficient replication, and a substantial amount of disagreement remains in the literature.

The lack of consensus of results among laboratories can be attributed at least in part to differences in subject populations. Often the HR subjects studied are beyond the age of risk, or the screening criteria rule out potential prealcoholics. Furthermore, the definition of increased risk that these studies have in common is that at least the father must have been an alcoholic. However, density of alcoholism within the family is variable across studies. If only the individual's father and no other first- or second-degree relatives are alcoholic, this may not mean that he is at increased genetic risk for alcoholism but may represent a phenocopy or sporadic case. Environmental influences must be taken into account. Furthermore, the criteria for diagnosis of alcoholism in the father and the manner in which his alcoholism is assessed contribute to differences in samples studied. Therefore the HR subjects in some studies are offspring of heavy or problem drinkers as well as alcoholics. In addition, differences in selection criteria for the control group also determine whether differences between HR and LR groups will be found. As alcoholism is a heterogeneous disease, HR groups in different studies may be composed of different numbers of offspring of different types of alcoholism.

The various types of prealcoholics may manifest different electrophysiological patterns before and after alcohol administration. As different studies often yield different results, this underscores the likelihood that alcoholism is a clinically heterogeneous disease with possible genetic heterogeneity. Therefore, subject selection remains a major problem in HR research. Ideally, the HR sample should consist of young children without prior exposure to alcohol who are offspring of alcoholic fathers from families in which alcoholism is prevalent; these alcoholic fathers should be diagnosed directly, and other psychiatric disorders should be eliminated.

Electrophysiological measures have an advantage in that they can provide indices of both trait and state characteristics. The trait indices perhaps provide phenotypic markers (e.g., P3 amplitude, high-frequency beta) distinguishing subjects at risk for alcoholism without the administration of alcohol. The electro-

physiological measures of state characteristics, namely how an individual's EEG and ERP respond to alcohol (changes in alpha and N1 amplitude) also distinguish HR from LR groups; these perhaps also represent vulnerability markers for alcoholism. It is possible that these electrophysiological measures may be useful in distinguishing different subgroups at risk for alcoholism. Future studies focusing on individual differences in electrophysiological measures before and after alcohol administration will help identify individuals at risk for specific types of alcoholism.

In order to determine whether these electrophysiological measures provide phenotypic markers of alcoholism, longitudinal studies will be needed to assess individuals as they pass through the age of risk. At present, there is not yet any compelling evidence demonstrating that those individuals manifesting a low P3 amplitude are in fact the ones who go on to become alcoholics. Longitudinal family studies are underway examining alcoholic and nonalcoholic families to determine which family members become alcoholic as they pass through the age of risk. It is hoped that with this approach the link between measures of risk and the development of alcoholism will be elucidated.

The foregoing review suggests that electrophysiological measures may serve as phenotypic markers for alcoholism. It is not suggested that these phenotypic markers are necessarily specific for alcoholism, nor is it suggested that all individuals manifesting these "markers" will necessarily go on to abuse alcohol. There is evidence, however, that individuals at risk for alcoholism (sons of alcoholic fathers) can be distinguished from those not at risk for alcoholism on electrophysiological measures, both without the ingestion of alcohol and in response to alcohol challenges. As the electrophysiological measures are genetically determined, these data imply that a predisposition or vulnerability to alcoholism is inherited. The role of environment and the gene-environment interaction are not to be minimized in determining whether an individual manifesting this predisposition goes on to abuse alcohol.

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