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Genetic Basis of Event-Related Potentials and Their Relationship to Alcoholism and Alcohol Use

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Event-related potentials (ERPs) are sensitive to the effects of acute and chronic alcohol administration on the brain, including intoxication, tolerance, withdrawal, and long-term abstinence. In general, intoxication is characterized by decreases in ERP amplitudes, particularly the N1 component (Bierley et al., 1980; Porjesz and Begleiter, 1993), as well as delayed central conduction time of both the brainstem auditory evoked potential (BAEP) (Chu et al., 1978; Squires et al., 1978*a,b*); and the so-called P3 component of the long latency evoked potential (Schuckit et al., 1988; Porjesz and Begleiter, 1993). When tolerance develops, the delayed central conduction in the BAEP is less pronounced (Chu et al., 1978; Squires et al., 1978*a,b*; Zilm et al., 1981) and P3 latency recovers more quickly (Schuckit et al., 1988; Porjesz and Begleiter, 1993). Withdrawal is marked by increases in ERP voltages as well as shortened BAEP latencies, suggesting the presence of an underlying central nervous system (CNS) hyperexcitability (Porjesz et al., 1976; Begleiter and Porjesz, 1977, 1979; Chu et al., 1978; Squires et al. 1978*a,b*; Begleiter et al., 1980*a*; Hunter and Walker, 1980; Romani and Cosi, 1989; Noldy and Carlen, 1990; Neiman et al., 1991). Long-term abstinence after chronic alcohol intake is characterized by reduced ERP amplitudes (hypo reactivity) and prolonged BAEP latencies and slower central conduction times (Begleiter et al., 1981; Porjesz and Begleiter, 1983, 1985). In addition, some characteristics of the ERP appear to represent invariant electrophysiologic signatures that are genetically influenced. Therefore, ERPs provide a sensitive means to assess both state and trait variables involved in alcoholism and alcohol consumption.

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For many years, it had been believed that all the ERP characteristics observed in alcoholics were due to the neurotoxic effects of alcohol on the CNS. More recently, however, new data suggest that some ERP characteristics observed in alcoholics are under genetic control and precede the development of alcoholism and may be markers of a predisposition to alcoholism. In the last few decades, low-amplitude P3 components have been reported in abstinent alcoholics (Porjesz and Begleiter, 1996). Although these low P3 voltages had been believed to be due to neurotoxic effects of alcohol on the CNS, evidence indicates that this is not true. We focus on the P3 amplitude and its relationship to alcoholism and to its genetic predisposition.

VISUAL P3 IN ALCOHOLICS

Years ago, we studied the P3 component in abstinent alcoholics with a visual paradigm involving geometric shapes (Porjesz et al., 1980). Rare and frequent geometric shapes (e.g., triangle, square) and rare novel irregular shapes were interspersed in a random sequence, and the subject was instructed to press a button to the occurrence of the rare geometric shape only. Target and nontarget stimuli were alternated in blocks enabling the recording of ERPs to the same shape (e.g., triangle) when it was a target and when it was the nontarget. Using this visual target-selection paradigm, we noted that alcoholics manifested reduced or absent P3 components to the target stimuli, without latency delays. This finding was most pronounced over parietal areas where the P3b is maximal (Ritter et al., 1968; Simson et al., 1977*a,b*). Furthermore, whereas controls manifested enhanced late P3 components to target as compared with nontarget stimuli, alcoholics manifested similar low-amplitude P3 waves with the same P3 latencies to both stimuli. Therefore, the two major ERP aberrations manifested by alcoholics are the lack

of differentiation between their cerebral responses to relevant and irrelevant inputs and the reduced amplitudes of their event-related activity.

The finding of reduced P3 amplitudes in alcoholics in visual oddball paradigms has been replicated in several laboratories (Emmerson et al., 1987; Patterson et al., 1987; Porjesz et al., 1987*a*; Pfefferbaum et al. 1991). In another visual oddball P3 paradigm using line stimuli, the relationship between the difficulty of discrimination and the amplitude of P3 in alcoholics was studied (Porjesz et al., 1987*a*). P3 components were obtained to two targets: a target that was easy to discriminate and positioned 90° from the vertical nontarget and a target that was difficult to discriminate (positioned only 3° from the vertical nontarget). As before, P3 amplitudes were significantly decreased in alcoholics, a finding more apparent for the easy 90° target than for the difficult 3° target. Furthermore, the amplitude of P3 was significantly larger to the 90° target than to the 3° target in controls but not in alcoholics, a finding in concordance with results of many other ERP studies which have demonstrated that more deviant rare stimuli (i.e., more easily discriminated from the background), produce larger P3 amplitudes (Ritter et al., 1972; Johnson and Donchin 1978; Ruchkin and Sutton 1978; Ford et al., 1979; Towey et al., 1980). The lack of P3 amplitude difference in the alcoholic group based on the difficulty of discrimination may indicate that they are more uncertain of the correctness of their decision than controls, because they appear to stress speed over accuracy. [Their reaction times (RTs) were faster and they made more errors than controls.] In contrast to controls, alcoholics did not manifest significant differences in P3 amplitude between target and nontarget stimuli. (This paradigm is more likely to elicit a P3-like component to the vertical nontargets because they are so similar to the 3° targets; therefore, each nontarget is viewed as a potential difficult target.)

Using a visual oddball task, Emmerson et al. (1987) reported that only the peak-to-peak amplitude of N2–P3 differentiated alcoholics from nonalcoholics. To rule out age effects, Emmerson et al. (1987) examined only alcoholics who were aged <40 years. Furthermore, they studied alcoholics who were abstinent for at least 1 month to rule out acute intoxication and withdrawal effects. Similarly, both Patterson et al. (1987) and Pfefferbaum et al. (1991) reported decreased P3 amplitudes to visual target stimuli in oddball tasks in the absence of latency delays. Results of these visual oddball studies in alcoholics all indicate that alcoholics manifest reduced P3 amplitudes to attended target stimuli.

In addition to standard visual oddball tasks, other visual P3 tasks elicit diminished P3 amplitudes in alcoholics (Porjesz and Begleiter, 1993, 1996). Using a go/no-go visual paradigm, Pfefferbaum et al. (1987) reported lower P3 amplitudes in alcoholics under go conditions but not under no-go conditions. In addition, the scalp distribution was flatter for alcoholics for the go condition but not the no-go condition. Ciesielski et al. (1985) reported lower peak-to-peak N2–P3 amplitudes with a visual memory paradigm and different hemispheric latency distributions between alcoholics and controls.

In another visual P3 paradigm involving incentive factors, Porjesz et al. (1987*b*) reported lower P3 amplitudes to equiprobable high-incentive stimuli in alcoholics as compared with controls, without latency delays. Latency corrected average procedures indicated that these results were not due to latency jitter in the average, but rather were due to lower single-trial voltages. This result was replicated by Pfefferbaum et al. (1991) in both visual and auditory oddball paradigms.

We investigated the relationship between visual P3 amplitude and structural brain damage as assessed by computed tomography (CT) scans in our laboratory using the geometric shape paradigm described above (Begleiter et al., 1980*b*). Two groups of alcoholics were studied: those exhibiting severely widened cortical sulci, (Pos-CT) and those who did not manifest enlarged cortical sulci (Neg-CT). The two groups did not differ in terms of age, education, or duration or amount of alcohol consumption. Alcoholics in the Pos-CT group manifested significantly lower P3 amplitudes to target stimuli than did alcoholics without evidence of widened cortical sulci (Neg-CT). However, neocortical shrinkage alone cannot explain the results of diminished P3 amplitudes in alcoholics, because both alcoholics with and without CT evidence of cortical atrophy manifested the same electrophysiologic deficits relative to normal controls.

Evidence from intracranial recordings in humans implicates both the medial temporal lobe (Halgren et al., 1980; Wood et al., 1980, 1984; McCarthy, 1985; Stapleton, 1985; Smith et al., 1986) as well as source or sources in the frontal lobe (McCarthy, 1985) as contributing to P3 generation. These findings, coupled with the rather small effect of unilateral temporal lobectomy on scalp P3 during auditory discrimination tasks. (Wood et al., 1984; Stapleton, 1985) suggest that multiple brain sites contribute to the scalp P3.

AUDITORY P3 IN ALCOHOLICS

The P3 results from auditory paradigms are not as consistent as those with visual P3. In an early auditory oddball study in which speed of RT was stressed, Pfefferbaum et al. (1979) reported no difference in P3 amplitudes between an older sample of alcoholics and healthy controls, but did report that alcoholics manifested delayed P3 latencies. In contrast, Patterson et al. (1987) reported decreased auditory and visual P3 amplitudes to target stimuli in the absence of latency delays in a bimodal study. In a subsequent identical study, Parsons et al. (1990) replicated the N1 and P3 findings in male but not female alcoholics. We obtained similar results of P3 amplitude decrements in the absence of latency delays to auditory target stimuli (Porjesz et al., 1988; Cohen et al., 1995).

Pfefferbaum et al. (1991) also reported that P3 amplitudes were significantly reduced in alcoholics as compared with controls in both visual and auditory oddball paradigms. In agreement with results of Porjesz et al. (1987*b*), results of single-trial latency adjustment procedures indicated that these amplitude differences were due primarily to signal size differences between the two groups and not to greater single-trial latency variability. Single-trial analysis of P3 amplitude indicated that the reductions in amplitude were due to smaller voltages on individual trials, not to latency jitter or the number of P3s in the average. Furthermore, SD of single-trial P3 latencies indicated that there were no significant differences between groups for either the auditory or visual paradigm.

In the present study, P3 latencies to attended auditory targets were delayed in alcoholics; this was not the case for attended visual targets or unattended rare auditory stimuli in the same subjects. Our study helps clarify earlier differences in the literature regarding whether alcoholics manifest P3 latency delays in oddball tasks. Latency and RT delays were reported to attended targets in alcoholics as compared with controls in auditory (Pfefferbaum et al., 1979) but not visual oddball paradigms (Pfefferbaum et al., 1987; Porjesz et al., 1980). However, visual P3 latency delays in alcoholics have been documented in an easy but not in a difficult discrimination task (Porjesz et al., 1987*a*), which suggests that P3 latency delays in alcoholics, rather than being modality specific, occur only during easy discriminations between targets and nontargets. Auditory oddball paradigms tend to be easier than visual paradigms. Although in the visual line discrimination study controls manifested significantly earlier P3 latencies to easy discriminations than to difficult discriminations, alcoholics did not manifest differences in P3 latency depending on task difficulty; in alcoholics, the P3 latency delays to the easy targets were prolonged to latencies comparable to a difficult discrimination task (Porjesz et al., 1987*a*). These results suggest that alcoholics, in contrast to controls, find both tasks difficult and adopt an undifferentiated mode of responding regardless of task requirements.

The most consistent electrophysiologic measure that differentiates alcoholics from healthy controls is the decreased P3 amplitude of alcoholics to targets in visual tasks at the Pz electrode. Although these findings have also been reported in the auditory modality, they are not as robust. Evidence indicates that the visual and auditory P3 are generated at different brain loci. Furthermore, many different kinds of P3 are elicited under different experimental conditions with different brain generators (Ruchkin et al., 1990).

P3s TO UNATTENDED STIMULI: P3A

The P3 components discussed thus far are obtained to attended task-relevant stimuli, to which the subject is required to make some response. However, automatic paradigms in which the subject is not asked to attend to rare deviant stimuli also elicit a different P3 with a more frontal topography (P3a). Although most attention has been focused on the attended P3b tasks in which it is necessary that the subject attend to the target selection (control processes), a few investigators have studied automatic processes in which the subject does not attend to the processing of rare stimuli (P3a). In an inattentive auditory oddball task, Pfefferbaum et al. (1991) reported that although P3 amplitudes to rare unattended stimuli were smaller in alcoholics than in controls, this result only approached significance. Using a larger sample size in an almost identical automatic auditory oddball task in our laboratory, Realmuto et al. (1993) reported that alcoholics manifested significantly lower P3 amplitudes than controls to rare unattended tones.

Alcoholics appear to be less able to distinguish deviant stimuli automatically from repetitive background stimuli, suggesting that simple processes of template match/mismatch are impaired. Either the template for comparison is not formed or retained or the match/mismatch processes themselves may be impaired in alcoholics. These results suggest deficits in automatic as well as control processes in alcoholics, although possibly not to the same extent in unattend conditions as in attend conditions.

In a study relating P3 amplitude and magnetic reso-

nance imaging (MRI), Ford et al. (1994) report that P3s recorded during both automatic and effortful attention correlated with frontal and parietal gray matter volumes. As reviewed earlier, Begleiter et al. (1980*b*) reported that alcoholics with cortical atrophy on CT scan manifested lower P3 amplitudes than alcoholics without cortical atrophy. Because alcoholics manifest frontal lobe damage (Oscar-Berman and Hutner, 1993), the reduced P3 amplitudes in alcoholics may be a manifestation of frontal damage.

FEMALE ALCOHOLICS

Most studies in which the effects of alcoholism were examined have focused exclusively on male alcoholics, partly because, until recently, the number of reported female alcoholics was low. However, because the number of female alcoholics has been increasing, more recent studies have been focused on female alcoholics. Parsons et al. (1990) reported that although male alcoholics manifest low P3 amplitudes, female alcoholics do not differ from normal subjects with regard to P3 amplitude. Hill and Steinhauer (1993*a*) reported that female alcoholics showed significant deficits in P3 amplitude as compared with female controls and their unaffected female siblings. Similarly, findings from an ongoing national study [Consortium on the Genetics of Alcoholism (COGA)] indicate that female alcoholic probands manifest decreased P3 amplitudes as compared with controls, though not to the same extent as males (Porjesz et al., 1996). These findings indicate that more investigations of female alcoholics are necessary to elucidate any differences.

RECOVERY OF ERP DEFICITS WITH ABSTINENCE

Because the ERP is extremely sensitive to the various aspects of alcoholism, (e.g., intoxication, withdrawal, long-term abstinence), determining the cause of the brain dysfunction manifested by alcoholics and the role of recovery is very difficult. Earlier ERP studies investigating recovery in alcoholics focused on the first 3 or 4 weeks after detoxification and overlooked the effects of medication administered during treatment (e.g., Coger et al., 1976; Salamy et al., 1980). In these studies, Antabuse (disulfiram) and/or Librium (chlordiazepoxide), both of which affect ERP voltages, was administered to recovering alcoholics. Increased ERP amplitudes have been reported in healthy volunteers who were treated experimentally with disulfiram (Peeke et al., 1979). Therefore, in these early studies it is difficult to ascertain whether the changes in amplitude reported were due to the effects of subsiding withdrawal, medication, an interaction between detoxification and medication, or recovery from brain damage. Furthermore, some of the studies (e.g., Coger et al., 1976), used a cross-sectional design in which different groups of alcoholics were tested at withdrawal or 3 to 4 weeks after withdrawal.

A study of auditory ERPs during withdrawal indicated that withdrawal was marked by increased amplitude of the N1–P2 component, particularly in seizure-prone alcoholics (Noldy and Carlen, 1990; Neiman et al., 1991). Similarly, Romani and Cosi (1989) reported larger N1–P2 components and shorter P3 latencies in an auditory oddball paradigm during withdrawal in alcoholics.

To study whether ERP aberrations manifested by alcoholics would recover with prolonged abstinence, abstinent alcoholics who were part of a long-term inpatient rehabilitation program were examined (Porjesz and Begleiter, 1985). Unmedicated alcoholics were studied at two timepoints in their recovery after withdrawal: at 3–4 weeks and again at 4 months. BAEPs and auditory and visual P3s (in a bimodal paradigm) were recorded identically on both occasions. At initial testing, BAEPs and central conduction times were delayed. However, after 4 months of abstinence, alcoholics manifested improved BAEP morphology, shortened latencies, and improved conduction times. These findings were replicated in Spain after a 1-year follow-up (Cadaveira et al., 1994).

Despite the improvement in BAEP with prolonged abstinence, there was no improvement in P3 amplitude after 4 months of abstinence in the same alcoholics. The waveforms and decreased P3 voltages to both auditory and visual stimuli were strikingly similar at initial test and final retest. These results suggest that the low P3 voltages may not be reversible, may precede alcoholism, or may recover more slowly after long abstinence periods. These findings were replicated in Spain by Grau et al. (1992), who reported that although P3 does not recover after 4 months of abstinence, N2 latency recovers completely. We have noted that alcoholics who are members of Alcoholics Anonymous still manifest low P3 amplitudes after extremely prolonged sobriety (3–10 years) (Porjesz and Begleiter, 1985), which suggests that low P3 amplitude is a trait marker that may reflect predisposing factors to alcoholism.

Glenn et al. (1993) showed that the latency of the N2 component of the ERP predicts whether an alcoholic will resume drinking. At initial testing, alcoholics

who would resume drinking manifested longer N2 latencies than those who did not resume drinking. In addition, Glenn et al. (1993) replicated findings from other laboratories also indicating that alcoholics manifest lower amplitude P3s as well as longer N2 latencies than controls. This N2 measure was not affected by family history for alcoholism, because both the resumer and abstainer groups had an equal number of persons with a family history of alcoholism. P3 amplitude may be an index of family history of alcoholism (described in section on Genetic Predisposition for Alcoholism and P3), whereas N2 latency is an index of the likelihood of resuming alcohol consumption. Therefore, in contrast to P3 amplitude, which appears to be a trait marker, N2 latency may represent a state marker. Furthermore, P3 does not recover after 4 months of abstinence, whereas N2 latency recovers completely (Grau et al., 1992).

The test–retest reliability of ERP measures over a 14-month period in controls and alcoholics was also investigated by Sinha et al., 1992, who reported that N1 and P3 amplitudes provided the most reliable measures in both groups, followed by N2 amplitude, N1 and N2 latency, and P3 latency. Because male alcoholics manifest decreased visual N1 and P3 amplitudes and increased N2 and P3 latencies at Pz (Porjesz et al., 1987*a*; Patterson et al., 1987; Parsons et al., 1990), test–retest reliability is the same for these groups.

GENETIC PREDISPOSITION FOR ALCOHOLISM AND P3

The brain abnormalities observed in alcoholics often are assumed to be due to the toxic effects of alcohol on the brain, nutritional deficits, or an interaction of alcohol and nutrition-related factors. However, accumulating evidence shows that some of these electrophysiologic aberrations may precede the development of alcoholism and may be related to a genetic predisposition to alcoholism. In this section, we review the literature dealing with the role of genetics and a family history of alcoholism as determinants of P3.

Family History of Alcoholism and P3: Alcoholics

Despite the characteristic low P3 amplitudes consistently reported in alcoholics, the role of chronic alcohol abuse on the diminished P3 voltages observed in alcoholics has come into question. Because the P3 component does not recover with prolonged abstinence (Porjesz and Begleiter, 1985), it is not likely to be related directly to the patient's drinking history (Pfefferbaum et al., 1991); instead, its characteristics appear to be genetically influenced (Polich and Burns, 1987; O'Connor et al., 1994; van Beijsterveldt, 1996; Katsanis et al., 1997; Almasy et al., submitted). It is important to examine the role of family history in determining the amplitude of the P3 component in alcoholics. In our laboratory, we have examined visual P3s in alcoholics with and without family histories of alcoholism and we have observed a significant difference in P3 amplitude between alcoholics and controls. Although alcoholics with a family history of alcoholism manifested lower visual P3 amplitudes than alcoholics without such histories, the results did not quite reach significance, possibly because the sample sizes were small. In a more recent auditory oddball study in our laboratory using larger sample sizes, Cohen et al. (1995) reported significant P3 amplitude differences between family history-positive (FHP) and family history-negative (FHN) alcoholics. Similarly, Patterson et al. (1987) reported that alcoholics with family histories of alcoholism manifested lower P3 amplitudes than alcoholics without family histories of alcoholism; however, this result was significant in the visual but not auditory modality, although it approached significance in the auditory modality.

Compelling evidence that family history of alcoholism rather than lifetime alcohol consumption determines whether alcoholics manifest low P3 amplitudes was reported by Pfefferbaum et al. (1991) using a PATH analysis. P3 amplitude to attended targets was significantly correlated with the number of relatives with "drinking problems" for both auditory and visual RT tasks. This decreased amplitude was independent of lifetime alcohol consumption in family history-positive alcoholics. Similar results are being obtained in the national COGA project in which P3 amplitudes from dense alcoholic families (i.e., at least 3 first-degree alcohol-dependent relatives) are compared with randomly ascertained control families (Porjesz et al., 1996). Members of densely affected alcoholic families were more likely to manifest low P3 amplitudes (2 SD below the mean) than controls (10 vs. 1%). Although 22% of alcohol-dependent members of densely affected alcoholic families manifested low P3 amplitudes, only 2.9% of the alcohol-dependent members of random control families did. Unaffected members of densely affected families were more likely to have low P3 amplitudes than were unaffected members of control families (6.8 vs. 0.1%).

Sufficient evidence appears to indicate that reduced P3 amplitudes observed in alcoholics are a function of family history of alcoholism and not of chronic alcohol

ingestion itself. Earlier differences between studies in terms of P3 results may be due in part to differences in compositions of alcoholic samples with respect to a family history of alcoholism. The findings that family history rather than drinking history determines the amplitude of P3 suggests that it is a trait measure that may be highly useful as a phenotypic marker for alcoholism. However, the studies investigated ERPs in alcoholics, in whom it is difficult to separate the consequences of years of chronic alcohol abuse from underlying factors. Therefore, a more direct approach to investigating etiology of brain abnormalities in alcoholics is to examine persons at risk who have not yet abused alcohol.

Family History of Alcoholism and P3: Offspring of Alcoholics

Population Genetic Studies

Evidence from population genetics studies indicates that sons of alcoholic fathers are four times more likely to develop alcoholism than are sons of nonalcoholic fathers (Goodwin and Guze, 1974; Goodwin, 1979) even when they are separated from their biologic parents soon after birth (Cloninger et al., 1981). Studies of male adoptees in Scandinavia indicate that the biologic rather than the adoptive parent is predictive of later drinking problems (Goodwin et al., 1973; Goodwin and Guze, 1974; Bohman, 1978; Cadoret and Gath, 1978; Cadoret et al., 1980). Furthermore, the concordance rate for alcohol abuse between identical twins is almost double the rate between fraternal twins (Kaij, 1960), and patterns of alcohol consumption have been reported to be highly concordant among identical twins (Partanen et al., 1966; Jonsson and Nilsson, 1968; Loehlin, 1972). The results of these population genetic studies suggest that genetic factors predispose sons of alcoholic fathers to alcoholism (Hesselbrock, 1995). More recently, female offspring were also determined to be at risk. In a recent comprehensive review of the literature on the genetic epidemiology of alcoholism, Hesselbrock (1995) concluded that the body of evidence suggesting that genetic factors influence the risk for alcoholism is overwhelming. Overall, in these compelling studies, investigators estimate that genetic effects may account for 40–60% of the variance in the liability for development of alcoholism. Together, the studies suggest that genetic factors may be involved in a predisposition to alcoholism.

The identification of a suitable biologic marker or markers that are genetically transmitted could elucidate the genetic factors involved in the etiology of alcoholism. Brain function probably is involved in a genetic predisposition to alcoholism, and electrophysiologic events such as the P3 component of the ERP may serve as biologic markers. Much evidence indicates that P3 amplitude is genetically influenced (Polich and Burns, 1987; Rogers and Deary, 1991; O'Connor et al., 1994; van Beijsterveldt, 1996; Katsanis et al., 1997) (described in section on Genetics and ERPs). Identification of a genetically transmitted biologic marker or markers would provide more definitive evidence that the etiology of alcoholism involves genetic factors and also might elucidate the potential nature of the genetic factors.

P3 in Offspring of Alcoholics

For more than a decade, we have been studying ERPs in subjects at risk for alcoholism. In our first study, the high-risk (HR) group consisted of sons of alcoholic fathers aged 7–13 years who had no prior exposure to alcohol (Begleiter et al., 1984). Their fathers had been diagnosed with alcoholism (DSM-III) and had been in treatment for alcoholism. Boys whose mothers either ingested alcohol during pregnancy or who drank excessively after birth were excluded. Only boys with neither medical problems nor exposure to alcohol or other substances of abuse were included in this study. The low-risk (LR) group consisted of healthy normal boys matched for age and socioeconomic status to the HR subjects. They were included only if they had no prior exposure to alcohol or other substances of abuse and if they had no first- or second-degree relatives with a history of alcoholism or other psychiatric disorder. Exception for family history of alcoholism, the same exclusion criteria were used in both the LR and HR groups.

A complex visual head-orientation paradigm was used to elicit the P3 component. The target stimulus was a rarely occurring aerial view of the head with the nose and either the right or left ear present, rotated in one of two possible positions (up or down). These targets were interspersed randomly among nontargets (ovals). Subjects were required to press one of two microswitches to the targets, as quickly and accurately as possible, indicating whether the right or left ear was presented. In the "easy condition," the head was facing forward (nose up on screen) and the left or right ear appeared on the same side as 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 significantly smaller in the HR than in 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) performed on the data 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 that P3 amplitude is significantly reduced in boys at risk for alcoholism, without exposure to alcohol. Since the performance of the original study, these findings have been replicated in several laboratories, with use of the identical head orientation paradigm, both in postpubescent (O'Connor et al., 1986) and in prepubescent (Hill and Steinhauer, 1993*b*) boys at risk for alcoholism. In addition, these results have been replicated with other visual paradigms, i.e., in a continuous performance task (Whipple et al., 1988, 1991; Noble, 1990; Berman et al., 1993) and a line discrimination task (Porjesz and Begleiter, 1990). Furthermore, we obtained reduced P3 amplitudes in pre- and postpubescent males at risk for alcoholism using auditory tasks in our laboratory (Begleiter et al., 1987; Ramachandran et al., 1996).

Begleiter et al. (1987) studied another group of sons of alcoholics to determine whether the reduced P3 amplitude observed in HR subjects was modality or task specific. In a modified auditory oddball task, subjects pressed a button in response to rarely occurring tones presented at a random rate; accuracy was stressed over speed. Twenty-three matched pairs of FHP and FHN males aged 7–16 years were studied; they were carefully interviewed to ascertain that they had no exposure to alcohol or illicit drugs. The fathers of HR boys in this sample met the criteria for male-limited (type 2) alcoholism (Cloninger, 1987). They manifested early-onset alcoholism, a high rate of recidivism, often accompanied by petty criminality, and required extensive treatment. In addition, the HR boys were from families in which there was a dense history of alcoholism. As in the previous visual study, the FHP boys manifested reduced P3 amplitudes. In HR males in this auditory paradigm the reduced P3 voltages are suggested not to be task or modality specific; they appear to be present in auditory and visual paradigms under conditions of speed and accuracy.

Whipple et al. (1988, 1991) used a continuous performance test (CPT) to examine ERPs in prepubescent boys at high risk for alcoholism. In the first study, they used a visual paradigm consisting of a complex series of visual stimuli that changed along three dimensions—shape, color, and identity of a number; the subject silently counted each time a stimulus identically matched the one preceding it on all three dimensions. In agreement with both Begleiter et al. (1984, 1987) and O'Connor et al. (1986, 1987), Whipple et al. (1988) reported a reduction in the amplitude of the late positive complex (LPC), including a P3 component. Later studies in the same laboratory replicated the original findings (Noble, 1990; Whipple et al., 1991; Berman et al., 1993). A study by Berman et al. (1993) indicated that P3 amplitude in prepubescent boys predicted later substance abuse in adolescence. Four years after the initial electrophysiologic testing, the adolescents were administered a substance abuse questionnaire dealing with alcohol and drug use. P3 amplitudes of the lowest voltage at initial test (prepubescent) were associated with the highest substance use scores. These findings provide strong evidence that P3 amplitude in prepubescent boys may provide a vulnerability marker for development of later substance abuse disorders.

We recently replicated our original findings of reduced visual P3 voltages without administration of alcohol in an older sample (aged 18–23 years) of sons of male alcoholics (Porjesz and Begleiter, 1990). The sample consisted of 25 male offspring of carefully diagnosed (DSM-IIIR/RDC) male alcoholics and was selected from high-density alcoholic families (mean number of alcoholic family members = 4), excluding persons in whom alcoholism may have been sporadic. Furthermore, persons whose mothers abused alcohol before, during, or after pregnancy were excluded. Controls were matched with the sons of male alcoholics on the basis of age, education, and socioeconomic status. They were selected from families in which there was no history of alcohol abuse or alcoholism in any first- or second-degree relatives. FHP and FHN subjects were carefully matched on drinking history, including duration and quantity/frequency information.

We used another visuospatial paradigm involving easy and difficult line discriminations, a paradigm that had previously elicited low-voltage P3 amplitudes in abstinent alcoholics (paradigm and results are described in section on P3 in Alcoholics). The stimuli consisted of a nontarget (vertical line) and two targets: an easy target that deviated from vertical by 90° (horizontal line) and a difficult target that deviated from vertical by only 3°. The subject pressed a button as quickly as possible (RT) to all nonvertical stimuli.

The results indicated that P3 amplitude before alcohol ingestion was significantly lower in HR subjects than in controls. This result replicates our previous findings (Begleiter et al., 1984, 1987) of lower voltage P3s in an older sample of HR males, as well as the

findings of O'Connor et al. (1986, 1987) and Whipple et al. (1988, 1991). The largest differences in P3 amplitude between groups occurred to the easy target, to which LR subjects manifested extremely high voltages. These results are identical to those we obtained in alcoholics with the same paradigm in which the easy target elicited the greatest significant difference in P3 amplitude between groups (Porjesz et al., 1987*a*). This P3 amplitude difference between groups was most apparent at Pz and Cz electrodes.

Female Offspring of Alcoholics

Most studies dealing with electrophysiologic measures in subjects at risk for alcoholism have focused on males only. The results of studies of female offspring have been less consistent. Hill and Steinhauer (1993*b*) studied P3 responses in both male and female pre- and postpubertal offspring of male alcoholics using the visual discrimination task designed by Begleiter et al. (1984). They replicated the P3 amplitude findings of Begleiter et al. in prepubescent boys, but did not find that pre- or postpubescent females manifested lower P3 amplitudes; neither did postpubescent males. Although lower P3 amplitudes were not reported in female offspring of male alcoholics with use of this visual paradigm (Hill and Steinhauer, 1993*b*), they were reported in female offspring of female alcoholics in a more recent report in which an auditory paradigm was used (Hill et al., 1995).

Recently, data from the large national COGA study, with a very large sample size, showed lower P3 amplitudes in female offspring of male alcoholics from dense alcoholic families, although not to the same degree as in males (Porjesz et al., 1996). Offspring of female alcoholics were excluded from the analysis to avoid the effects of prenatal alcohol exposure. Not all offspring of alcoholics have low P3 amplitudes, but as compared with the rest of the population, a large percentage of them do. Evidently offspring in densely affected alcoholic families are at increased risk to manifest low P3 amplitudes (Porjesz et al., 1996).

P3 and Alcohol Consumption in Offspring of Alcoholics

Findings relating alcohol consumption history to P3 characteristics do not appear to be robust, even in studies from the same laboratory. Previous alcohol consumption has been shown to correlate with P3 amplitude only, particularly in FHP subjects (Polich and Bloom, 1987), to correlate with P3 latency only (Polich and Bloom, 1988), and to be uncorrelated with any previous drinking variables (Polich et al., 1988). The relationship between P3 characteristics and drinking history remains an unresolved issue in other laboratories as well: Some studies indicate a correlation between drinking history and P3 latency, and others indicate no relationship between any P3 characteristic and drinking history (Porjesz and Begleiter, 1993, 1996).

After administration of alcohol, differences in P3 characteristics have also been observed between subjects at high and low risk for alcoholism. Significant P3 amplitude decreases in HR subjects as compared with LR subjects were reported after both alcohol and placebo ingestion by Elmasian et al. in San Diego (1982); they explained their results in terms of differential expectancies for alcohol characterized by different brain events. Unfortunately, different sets of subjects were used for each condition, and there were only five pairs of subjects per group, making interpretation of the data difficult. This group of investigators did not replicate the initial placebo effect in a later study. Schuckit et al. (1988) reported that P3 latency delays returned to baseline values more rapidly in FHP men than in FHN men after a high dose of ethanol (1.1 ml/kg). Similar results in P3 latency after ethanol ingestion by HR males in a visual task have been obtained in our laboratory. Sons of alcoholic fathers manifest abnormal P3 component amplitudes and normal N1 amplitudes and P3 latencies before alcohol ingestion (Porjesz and Begleiter, 1990). However, after alcohol intake, they exhibit quicker recovery of both N1 amplitudes and delayed P3 latencies than do LR subjects. These findings suggest that some electrophysiologic differences between FHP and FHN individuals are apparent only in response to ethanol challenges, possibly representing tolerance in the FHP subjects that may be innate.

Summary and Discussion of P3 in Offspring of Alcoholics

The results of studies of P3 amplitude indicate that they are reduced in voltage in older and younger HR males both to attended and unattended stimuli and to easy and difficult discriminations in visual and auditory modalities with and without alcohol administration. Despite the general consensus that P3 amplitudes are of lower voltage in HR males, some studies that have failed to replicate such findings (Polich et al., 1994). Mostly these are studies by various groups of investigators in San Diego examining ERPs in college students with positive family histories of alcoholism. A

recent meta-analysis (Polich et al., 1994) of all the research on P3 characteristics in subjects at risk indicates that although P3 amplitude generally is of lower voltage in subjects at risk for alcoholism, it is most likely to be evident in young prepubescent males performing difficult visual tasks. The results in older offspring appear to be more variable, particularly those involving auditory easy tasks (Polich et al., 1994).

Although discrepancies in results have been hypothesized to be due to task difficulty, recent evidence is equivocal. Identical results have been obtained with tasks at different levels of task difficulty. The meta-analysis of Polich et al. (1994) indicated that task difficulty is a factor in determining P3 results between FHP and FHN groups; i.e., the more difficult the task, the more likely the difference between groups. However, "task difficulty" is not necessarily a continuum along which P3 results can be explained. Some aspects of task difficulty alter P3 characteristics, whereas others do not; e.g., difficulty of stimulus discrimination alters P3 characteristics, whereas response selection difficulty does not.

The lack of consensus of results among groups of investigators can be attributed at least in part to differences in subject populations. The only definition of risk for alcoholism that the studies share is that at least the father must have been an alcoholic. Therefore, the density of alcoholism within the family fluctuates across studies. Benegal et al. (1995) reported that P3 amplitude in offspring of alcoholics was inversely related to the family density for alcoholism. If only the individual's father and no other first- or second-degree relative is alcoholic, the genetic risk for alcoholism may not be increased but a phenocopy or sporadic case may be indicated. Furthermore, the clinical criteria for diagnosis of alcoholism in the father and the manner in which his alcoholism is assessed contribute to differences in the samples studied. Criteria in some studies require multiple persons to be affected with alcohol dependence, some require that alcoholism be multigenerational, and others require only one symptom of alcoholism in the father to constitute qualification for inclusion in an HR group. Furthermore, the assessment of alcoholism differs among studies, with some groups of investigators obtaining only indirect information regarding the father from the son. Therefore the HR subjects in some studies may include offspring of heavy drinkers or problem drinkers. This factor weakens the loading of familial alcoholism, making it less likely that significant results between groups will be obtained. Problems such as comorbidity for other psychiatric problems are also treated differently in different studies; persons manifesting comorbid psychiatric diagnoses (e.g., antisocial personality or affective disorder) may be excluded from some studies and included in others. Because alcoholism is a heterogeneous disease, HR groups in different studies may be composed of different numbers of offspring from families with different types of alcoholism (e.g., type 1 and type 2); these subtypes of alcoholism may manifest different electrophysiologic patterns before and after alcohol administration. Often the HR subjects studied are beyond the age of risk or the stringent screening criteria rule out potential prealcoholics. Furthermore, environmental influences must be taken into account; variables such as socioeconomic status, education, and age may affect the results obtained. In addition, differences in selection criteria for the control group may also determine whether differences between HR and LR groups will be detected. Therefore, subject selection remains a major problem in HR research, and more agreement may exist in the literature dealing with subjects at risk for alcoholism than had been heretofore suspected (Polich et al., 1994).

Combined, the reviewed data indicate that the low P3 amplitude apparently is a robust finding that characterizes individuals at risk for alcoholism, prior to any alcohol exposure. Low P3 amplitudes are not due to the neurotoxic effects of alcohol on the brain, and they do not recover with prolonged abstinence. As this review indicates, much evidence suggests that the P3 amplitude has utility as a potential phenotypic marker for alcoholism. Low P3 amplitude in young boys has been shown to predict future substance abuse in adolescents (Berman et al., 1993; Hill et al., 1995). P3 amplitude in alcoholics and HR individuals has been demonstrated to be directly related to the number of affected relatives in the family (Pfefferbaum et al., 1991; Benegal et al., 1995). Therefore, family history of alcoholism and not alcohol history correlates with P3 amplitude. For this finding to be considered as a phenotypic marker for alcoholism, however, certain criteria must be met. The most important criterion is that it be heritable, and described in the following section, evidence shows that the P3 component amplitude is a heritable property of this ERP component.

Genetics of EEG and ERPs

Much evidence indicates that characteristics of both the EEG and ERP are genetically determined (van Beijsterveldt and Boomsma, 1994). The production of fast EEG activity has been demonstrated to be genetically transmitted (Vogel, 1970; Young et al., 1972;

Propping, 1977). In various studies, Vogel has reported the hereditary nature of several EEG variants (monomorphic alpha, low-voltage EEG, EEG with alpha and beta diffusely mixed, EEG with frontoprecentral beta) (Vogel, 1970; Vogel et al., 1986). Vogel (1970) maintains that the low-voltage and regular alpha EEG are inherited in an autosomal dominant mode, whereas the poor alpha or diffuse beta variants are under polygenic control. Spectral analyses of EEG have shown higher correlations for Mz than Dz twin pairs (Dumermuth, 1968; Lykken et al., 1974, 1982; Stassen et al., 1987). Stassen et al. (1987) showed that the spectral patterns of Mz twins were almost as similar as those of the same individual tested twice, whereas the Dz twin patterns were significantly more similar to each other than were patterns in unrelated individuals. These findings were confirmed in a later study (Stassen et al., 1988) examining EEGs of Mz and Dz twin pairs reared apart. In addition to this strong evidence that EEG patterns are genetically determined, evidence also shows that ERPs are under genetic control. Monozygotic twins manifest ERP waveforms that are as concordant with each other as are ERPs obtained from the same individual tested twice (Dustman and Beck, 1965; Surwillo, 1980). ERPs recorded to flashes of different intensities have been reported to be under genetic control (Buchsbaum and Pfefferbaum, 1971). Higher heritabilities have been reported for the endogenous ERP components than for the exogenous components (van Beijsterveldt and Boomsma, 1994).

The P3 component of the ERP is more similar in identical twins than in unrelated controls (Polich and Burns, 1987) and fraternal twins (Rogers and Deary, 1991; O'Connor et al., 1994; van Beijsterveldt, 1996; Katsanis et al., 1997). Evidence that P3 amplitude is genetically transmitted derives from both twin studies and family studies. O'Connor et al. (1994) reported auditory P3 amplitude Mz twin heritability to range between 0.49 and 0.60 at posterior leads. Similar heritabilities based on a large twin study were recently reported for visual P3 amplitude (van Beijsterveldt, 1996) and most recently in a study using a visual head-orientation oddball paradigm (Katsanis et al., 1997).

In an ongoing large national family project (COGA), several studies have indicated comparable heritabilities for the visual P3. Based on a large sample of 163 randomly ascertained COGA control families with offspring aged >16 years (687 individuals), Daw et al. (1995) performed a comingling analysis on the amplitude of the visual P3 component to target stimuli recorded at the Pz lead (the condition under which measurement of the P3 amplitude is optimal). In testing for admixture, the P3 amplitude was shown not to be due to a major gene, but instead could be accounted for by a single skewed distribution with an estimated heritability at 0.50 in the general population. More recently, Almasy et al. (submitted) estimated the heritability of P3 amplitude in 604 individuals from 100 pedigrees ascertained as part of the COGA project. They reported significant heritabilities for both visual and auditory P3 amplitudes to target stimuli; however, heritabilities were higher for visual than for auditory P3 amplitudes. Heritability estimates ranged from 0.43 to 0.54 for visual posterior leads and from 0.27 to 0.40 for auditory leads, with which the highest heritabilities were at central/frontal scalp locations. Most recently, the COGA project has undertaken various linkage analyses, including studies to identify the genetic bases of ERPs (Begleiter et al., in press). Two methods were used: SAGE Sibpal (1994), a nonparametric method program using two-point identity by descent (IBD) methods, and the SOLAR (Sequential Oligogenic Linkage Analysis Routines) method (Blangero and Almasy, 1997), a multipoint quantitative linkage package using variance components. The genetic analysis of the COGA sample is based on 990 persons from 105 densely affected families, comprising 300 sibpairs. Approximately 275 highly polymorphic DNA markers were genotyped in these alcoholic families, with a mean intermarker interval of 20 cM. The COGA visual P3 linkage analysis was based on 604 persons from 100 pedigrees. Two "hotspots" of significant linkage were identified, one on chromosome 6 at Cz and related leads and the other on chromosome 2 at O2 and related posterior leads. Because these results were obtained at adjacent markers and leads, they apparently do not represent spurious cases. Currently, flanking markers are being placed in these regions. In a recent dissertation in Holland, Molenaar and Boomsma's group (van Beijsterveldt, 1996) studied the visual P3 in a large sample of twins using a multivariate genetic analysis approach. They reported two independent factors to account for visual P3 amplitude, i.e., one factor that influences all the electrodes and a second factor that influences occipital leads. These chromosome 2 findings for the posterior leads may represent this second occipital factor.

The detection of significant linkage for the P3 amplitude of the ERP suggests that the P3 amplitude provides a phenotypic marker that has genetic underpinnings. Understanding the genetic control of brain electric activity may provide clues about cerebral function and shed light on pathogenic mechanisms of neurologic and psychiatric disorders in which impairment

of brain electric activity is apparent (e.g., low P3 amplitudes observed in alcoholism).

IMPLICATIONS

As our review indicates, one of the most robust electrophysiologic findings that characterizes alcoholics and persons at risk for alcoholism is the reduced voltage of their P3 components of the ERP. Such persons tend to respond to both the "significant" or target stimulus and to the nonsignificant nontarget stimuli similarly, with low P3 amplitudes. In contrast, healthy control subjects respond differentially to target and nontarget stimuli, manifesting extremely large P3s to the targets. This undifferentiated mode of responding to all stimuli in alcoholics and HR subjects suggests that they are unable to utilize available information, reflecting an inefficiency in brain processing. In contrast to healthy individuals who set up a template of nontarget stimuli against which to match or not match each new stimulus, alcoholics and subjects at risk evaluate each incoming stimulus anew, which suggests that their template for match–mismatch decisions is not laid down, is lost, or is not readily available. This inability to respond electrophysiologically differentially to incoming stimuli suggests problems in electrophysiologic disinhibition in alcoholics and HR individuals. Evidence from monkey studies indicates that differential inhibition facilitates the efficient processing of a given stimulus; there is less neuronal firing to repeated stimuli, suggesting inhibition of masses of neurons (Miller et al., 1991) and increased synaptic efficiency. The more probable a stimulus, the smaller the P3, and the more subjectively improbable a stimulus, the larger the P3. Alcoholics and subjects at risk do not manifest this differential neuronal inhibition.

It is tempting to speculate about the relationship between this underlying neurophysiologic disinhibition and the behavioral disinhibition commonly observed in alcoholics and their offspring. Alcoholism has been associated with disinhibited psychopathology, including antisocial and impulsive personalities, characterized by increased drug and alcohol use and sexual activity, unstable work records, and delinquency. Furthermore, alcohol consumption in young adults of both sexes has been correlated with the Disinhibition Scale, which describes a need to disinhibit social behaviors. Longitudinal studies of childhood and adolescent precursors of adult alcohol abuse consistently identify a cluster of behavioral traits described as disinhibited, undercontrolled, impulsive, or aggressive that significantly predict high levels of alcohol consumption or abuse (Cloninger et al., 1988). Both antisocial personality disorder (ASPD) and family history of alcoholism predispose persons to alcoholism, and persons in both these groups manifest low P3s (Hesselbrock et al., 1993). Together, the electrophysiologic results (i.e., low P3 amplitude in alcoholics and their offspring) suggest that aspects of brain dysfunction (i.e., lack of differential inhibition) may be involved in a predisposition for alcoholism. The genetic predisposition for alcoholism may be caused by an increase in CNS hyperexcitability in persons at risk.

These data suggest that these electrophysiologic 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 persons manifesting these "markers" will necessarily later abuse alcohol. However, evidence shows that persons at risk for alcoholism (sons of alcoholic fathers) can be distinguished from those not at risk for alcoholism by electrophysiologic measures, both without ingestion of alcohol and in response to alcohol challenges. Because the electrophysiologic measures are genetically determined, the data imply that a predisposition or vulnerability to alcoholism is inherited. The role of environment and the gene–environment interaction should not be minimized in determining whether a person manifesting this predisposition later abuses alcohol.

Longitudinal studies are in progress as part of the COGA project to retest all family members. The resultant data will be particularly informative in assessing the offspring of alcoholics from densely affected families as they pass through the age of risk for developing alcohol-related problems, including alcohol dependence. The COGA data predict that offspring of alcoholics who manifest P3 amplitudes in the low range are most at risk for developing alcoholism. Not all offspring of alcoholics are at risk for alcoholism. In the COGA project, no deficits in P3 amplitude were observed in children from randomly ascertained control families with only sporadic cases of alcoholism. Whether HR persons manifesting low P3 voltages are actually those who later develop the disease of alcoholism remains to be determined in longitudinal studies. It is hoped that this approach will elucidate the link between measures of risk and the development of alcoholism.

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