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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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What Is Inherited in the Predisposition Toward Alcoholism? A Proposed Model

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Background: The etiological factors associated with the predisposition to develop alcohol dependence remain largely unknown. In recent years, neurophysiological anomalies have been identified in young and adult offspring of alcoholic probands. These neuroelectric features have been replicated in several laboratories across many different countries and are observed in male and female alcoholics and some of their relatives and offspring. Moreover, these electrophysiological abnormalities are heritable and predictive of future alcohol abuse or dependence.

Methods: A model is presented which hypothesizes that the genetic predisposition to develop alcoholism involves an initial state of central nervous system (CNS) disinhibition/hyperexcitability. We propose that the event-related brain potential (ERP) anomalies reflect CNS disinhibition. This homeostatic imbalance results in excess levels of CNS excitability which are temporarily alleviated by the ingestion of alcohol. It is hypothesized that this hyperexcitability is heritable, and is critically involved in the predisposition toward alcoholism and the development of dependence. A brief review of the relevant literature is presented.

Results: Neurophysiological, neurochemical, and genetic evidence support the proposed model. In addition, strikingly similar observations between animal research and the human condition are identified. Finally, it is asserted that the proposed model is primarily biological in nature, and therefore does not account for the entire clinical variance.

Conclusion: A putative CNS homeostatic imbalance is noted as a critical state of hyperexcitability. This hyperexcitability represents a parsimonious model of what is inherited in the predisposition to develop alcoholism. It is our hope that this model will have heuristic value, resulting in the elucidation of etiological factors involved in alcohol dependence.

Key Words: P3, ERP, CNS Disinhibition, Genetic Predisposition.

ETIOLOGICAL FACTORS INVOLVED in the development of alcohol dependence remain unknown. Because of recent advances in genetic epidemiology, novel paradigms, and advanced neurobiological methods, the need for elucidating the pathogenesis of alcoholism among some patients seems to be hopeful. In this brief exposition, we present a hypothesis of what may be inherited in the predisposition toward alcoholism. When possible, we include experimental data, or in some cases, circumstantial evidence, and finally use these data to propose a model of alcohol dependence that would account for a certain proportion of the total disease variance.

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GENETIC INFLUENCE IN ALCOHOLISM

In a recent comprehensive review of the literature on the genetic epidemiology of alcoholism that included twin studies, family studies, and adoption studies, V. Hesselbrock (1995) concluded that "collectively, the body of evidence provides a powerful demonstration of the influence of genetic factors on the risk for alcoholism." In general, these compelling studies estimate that genetic effects may account for 40–60% of the variance in the liability for the development of alcoholism. The search for genes that influence the predisposition toward alcoholism is extremely difficult because we do not understand how genetic risk is transmitted, and we cannot identify carriers of genes in the absence of manifest symptoms. In addition, psychiatric diagnosis may create spurious heterogeneity, and does not inform us about the underlying biological mechanism. These shortcomings lead to false-positives as well as false-negatives, which result in the loss of statistical power when conducting a linkage analysis.

ENDOPHENOTYPE

An alternative to the use of clinical phenotypes is the identification of fundamental neurobiological or neurobehavioral characteristics associated with alcoholism—so-

called endophenotypes or intermediate phenotypes—whose manifestation may be more closely linked to gene expression (Gottesman and Shields, 1972). Many of the aforementioned problems could be alleviated with the use of a heritable biological endophenotype that could identify those individuals at genetic risk in the absence of overt manifest symptoms. Certain criteria must be met for a specific trait to be of use as an endophenotype:

1. Must be present in affected individuals
2. Must be present in unaffected relatives
3. Must be present in individuals known to be at high risk to develop alcoholism
4. Must have predictive power
5. Must be heritable
6. Should provide specific biological manifestations more directly linked to gene expression.

It is assumed that when an individual manifests the endophenotype, the probability of identifying a gene carrier is significantly increased. The ability to determine which family members are more likely to carry a gene significantly enhances our prospect of determining whether individuals with the putative genes can be identified with a genomic search. The endophenotype can be used in conjunction with diagnostic criteria to improve substantially phenotypic definition, which results in improved classification accuracy. Moreover, the putative endophenotype need not be strictly associated with a specific psychiatric disorder, but may be present in a number of disorders with a common genetic diathesis. Needless to say, our full knowledge of the biological mechanisms of the endophenotype would greatly enhance our understanding of etiological factors. The availability of a valid and reliable endophenotype would provide a valuable measure of genetic risk, and could result in the identification of predisposing genes.

THE P3 COMPONENT OF THE EVENT-RELATED BRAIN POTENTIAL

In the last three decades, several laboratories, which used neurophysiological methods, have identified a number of neuroelectric features that seem to be anomalous in abstinent alcoholics (Cohen et al., 1995; Emmerson et al., 1987; Parsons et al., 1990; Patterson et al., 1987; Pfefferbaum et al., 1987, 1991; Porjesz et al., 1980, 1987a, 1987b). In all of these studies, the primary finding was a decreased P3 component of the Event-Related Brain Potential (ERP) in abstinent alcoholics compared with controls. The P3 component is the third positive component of the ERP, occurring between 300–500 msec after the stimulus, and is usually obtained in response to a rare target stimulus (Fig. 1). This commonly observed low P3 voltage initially was assumed to be caused by the neurotoxic effects of chronic alcohol intake.

To determine whether ERP aberrations manifested by alcoholics would recover with prolonged abstinence, we

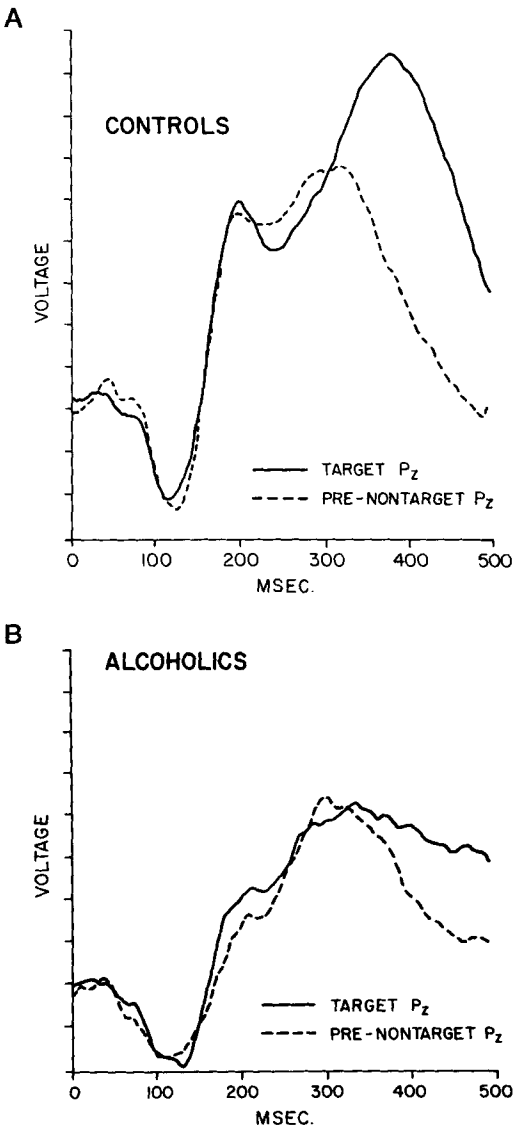

Fig. 1. *A* Averaged ERP recorded in response to target stimuli (solid line) and an equal number of nontarget stimuli (dashed line) in healthy control subjects. Large positive deflection to target stimulus occurring around 400 msec is the P3 component. Notice large difference in P3 voltage between target and nontarget stimuli in healthy subjects. *B* Averaged ERPs recorded in response to target stimuli (solid line) and an equal number of nontarget stimuli (dashed line) in alcoholics. Note the lack of difference in P3 voltage between target and nontarget stimuli in the alcoholic group.

examined abstinent alcoholics who were a part of a long-term inpatient rehabilitation program (Porjesz and Begleiter 1985). Despite the improvement in brainstem potentials with prolonged abstinence, there was no improvement in ERP morphology or P3 amplitude after 4 months of abstinence in the same alcoholic patients. The waveforms and decreased voltages to both auditory and visual stimuli were strikingly similar at the initial test and retest. Similar studies dealing with patients abstinent from 5 to 10 years resulted in identical findings. To us, these results suggested that the low P3 voltages may not be reversible and may antecede the development of alcoholism.

P3 IN HIGH RISK INDIVIDUALS

In 1980, we began a series of ongoing investigations to test the hypothesis that low P3s typically observed in abstinent alcoholics might be present in young boys with an alcoholic father and who come from a family with a high density of alcoholism. In 1984, we first published our findings which indicated that young boys at high risk (HR) of developing alcoholism manifested significantly lower P3 voltages compared with matched low risk (LR) boys coming from control families without first or second degree alcoholic relatives (Begleiter et al., 1984). The results of this study were rather striking because they were obtained without the use of an alcohol challenge or a placebo. These findings in young HR boys have now been replicated in a number of laboratories (Benegal et al., 1995; Berman et al., 1993; Hill et al., 1993; van der Stelt et al., 1998; Whipple et al., 1988, 1991), but have not been observed in a few studies (Hill et al., 1995; Polich and Bloom, 1988; Polich et al., 1988). In a comprehensive meta-analysis of all published high risk versus low risk studies, Polich et al. (1994) found that the strongest P3 group differences were obtained in young offspring with relatively difficult visual tasks and concluded that low voltage P3 may have predictive value as an index of vulnerability for alcoholism. The use of P3 as a putative phenotypic marker of risk for developing alcoholism is supported by results that indicate that the low amplitude component observed in alcoholics and in young HR boys is also present in young nonalcoholic adult males (Bauer et al., 1994; Hesselbrock et al., 1993; O'Connor et al., 1986; Porjesz and Begleiter, 1990; Ramachandran et al., 1996). Recent studies have demonstrated, in a compelling manner, that the P3 deficit in alcoholics and in HR individuals is proportional to the number of affected relatives in the family (Benegal et al., 1995; Cohen et al., 1995; Pfefferbaum et al., 1991). Equally important are two recent studies which indicate that low amplitude P3 in high risk individuals is predictive of future alcohol and substance abuse in adolescents (Berman et al., 1993; Hill et al., 1995). Finally, in a large Collaborative Study on the Genetics of Alcoholism (COGA), Porjesz et al. (1998) reported significant P3 deficits in alcoholic probands, affected and unaffected relatives, and young offspring, both male and female, from densely affected families.

Together, the aforementioned studies provide substantial evidence which indicates that the amplitude of the P3 component of the ERP is deficient in abstinent alcoholics. This low P3 voltage is correlated with the number of affected relatives in the family. Most importantly, it is also observed in some young prepubescent as well as young adult offspring of alcoholics. Finally, this P3 voltage deficit is present in some unaffected relatives of alcoholic patients, and its presence in young offspring may predict the future development of alcohol abuse or dependence. In brief, this neuroelectric feature of the ERPs may be considered as a putative phenotypic marker for the study of the genetic predisposition toward alcoholism. However, the use of this neurophysiological feature in genetic linkage depends in large measure on its heritability. Recent studies on the heritability of the P3 component of the ERP conducted in twins have shown consistent results with heritabilities ranging from 50–60% (Katsanis et al., 1997a; O'Connor et al., 1994; van Beijsterveldt, 1996). More recent family studies, using a large number of pedigrees, have also confirmed heritabilities ranging from 50–60% (Almasy et al., 1998). These heritability studies are most encouraging, and should allow us to use these neuroelectric features as putative phenotypic markers. However, before conducting a time-consuming and expensive linkage analysis that uses a large number of families with extensive pedigrees, it is important to assess the physiological significance of this novel quantitative phenotypic marker in relation to the qualitative diagnosis.

In addition to the robust finding of a low voltage P3 component in alcoholics and individuals at risk, these individuals also do not respond differentially to "significant" target and nonsignificant, nontarget stimuli, manifesting similar low P3 amplitudes to all stimuli. In contrast, healthy control subjects respond differentially to target and nontarget stimuli, manifesting extremely large P3s to the targets (Figure 1).

This undifferentiated mode of responding to all stimuli in alcoholics and high risk subjects suggests that they are unable to utilize available information, which reflects an inefficiency in brain processing. Furthermore, current source density (CSD) studies of P3 in our laboratory indicate that whereas healthy individuals manifest well-delineated bilateral sources of the visual target P3 at frontal and parieto-occipital areas, alcoholics do not manifest strong frontal sources; their sources and sinks are weaker and more similar across the scalp than controls, perhaps reflecting a lack of efficiency in brain function. This electrophysiological inability to respond differentially to incoming stimuli suggests problems in neurophysiologic disinhibition in alcoholics and subjects at risk (Porjesz and Begleiter, 1995, 1996, 1997, 1998). Studies in monkeys indicate that differential inhibition facilitates the efficient processing of a given stimulus; there is less neuronal firing to repeated stimuli, which suggests inhibition of masses of neurons (Miller and Desimone, 1991). 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, and hence must process each incoming stimulus anew.

P3 AS AN INDEX OF CNS INHIBITION

In keeping with various physiological explanations for the P3 component of the ERP (Desmedt, 1980; Lutzenberger et al., 1978), we have conjectured that low P3 voltage is an index of central nervous system (CNS) disinhibi-

tion (Cohen et al., 1997; Porjesz and Begleiter, 1996, 1997, 1998; Ramachandran et al., 1996). Several investigators (Halgren et al., 1986; Rockstroh et al., 1992; Smith et al., 1990; Woodward et al., 1991) have proposed that the P3 component of the ERP is largely caused by a widely distributed inhibitory event which operates under various processing functions. Several sources have been proposed, such as the temporal-parietal junction (Knight et al., 1989) and the magnocellular or intralaminar tuning mechanisms that regulate cortical excitability (Velasco et al., 1986; Yingling and Hosobuchi, 1984) which, in turn, could modulate the polarization of neocortical apical dendrites known to be the primary contributor to the scalp EEG (Elbert and Rockstroh, 1987). A somewhat different mechanism for controlling pyramidal cells by P3 has been proposed by Roberts et al. (1994). These investigators suggested that the P3 component of the ERP arises in part when propagation of lateral inhibition through the reticular nucleus decreases thalamocortical pathways and cortical projection sites not driven by the task stimulus relative to the pathways activated by the specific stimulus. Other investigators (Deecke et al., 1984) have invoked a resolution/relaxation hypothesis which asserts that the P3 positivity constitutes an inhibitory resolution of preceding excitatory negativity. Rockstroh and colleagues (1989) as well as Birbaumer et al. (1990) proposed that negative shifts in ERPs indicated enhanced excitability of neural networks, whereas positive shifts were indicative of decreased excitation. It may be hypothesized that slow positive potentials such as the P3 component of the ERP indicate an inhibitory process, namely a disfacilitated state of neuronal networks. The lack of CNS inhibition in individuals at risk of developing alcoholism can be conceptualized as an excess of CNS excitation.

This CNS hyperexcitability reflects a disequilibrium in the homeostatic mechanisms that control the critical CNS balance between excitation and inhibition. The recent findings from the COGA project support the hypothesis of the low P3 amplitude as an index of CNS disinhibition (Porjesz and Begleiter, 1998; Porjesz et al., 1998). With the use of latent class analysis, we have recently observed four easily discriminable classes which represent a severity dimension for alcohol dependence (Bucholz, unpublished data). Our data provide strong evidence that increased severity of alcohol dependence is inversely related to P3 amplitude. It is not just the most severe alcoholics whose amplitude of P3 is low in comparison with those who are unaffected, but the next most severely affected group also demonstrates a low P3 amplitude, albeit somewhat higher than the most severe group. In brief, it is those individuals with the highest endorsement probability for alcohol dependence who have the greatest proportion of low P3 amplitudes (Bucholz et al., 1998). A pleiotropic model has been suggested by the COGA results (Porjesz et al., 1998) where the genotype is assumed to indicate a low voltage P3 as a predisposing factor for the future development of a number of disinhibitory conditions such as alcoholism, substance abuse, attention deficit hyperactivity disorder, and antisocial behavior.

QUANTITATIVE TRAIT LOCI AND P3

To determine the genetic loci underlying the P3 component, linkage analyses have been performed on a large sample from families with a high density of affected individuals in the COGA project (Begleiter et al., 1998) using SOLAR (Blangero and Almasy, 1996), a multivariate, multipoint quantitative linkage analysis program that incorporates variance components. Visual P3 amplitudes were recorded from 19 electrodes for 607 individuals in 103 families who were genotyped using approximately 275 polymorphic DNA markers approximately 13.6 cM apart. "Hotspots" were identified on several chromosomes, with significant evidence of linkage [logarithm of odds (LOD) scores over 3.0] on chromosome 2, (LOD = 3.3) and 6, (LOD = 3.4). These significant results were sustained when rerunning the SOLAR analyses using the GAW (Genetic Analysis Workshop) map, a map with more evenly spaced, informative markers. More recently, we have added flanking markers to these significant regions and have found that the LOD scores improved for chromosome 2 (LOD = 3.4) and chromosome 6 (LOD = 3.7) using these dense maps. Together, these results from the COGA project suggest that the visual P3 amplitude provides a biological phenotypic marker that has genetic underpinnings. Understanding the genetic control of brain electrical activity may provide clues about cerebral function and shed light on pathogenic mechanisms of neurologic and psychiatric disorders in which such impairment of brain electrical activity is apparent (e.g., low P3 amplitudes observed in alcoholism).

Given the strong evidence for several quantitative trait loci that influence visual P3 amplitude (Begleiter et al., 1998), we wished to determine whether these loci also influenced the risk of alcoholism. Blangero and colleagues (Williams et al., 1998) have developed a bivariate procedure that allows for joint consideration of both the disease and quantitative precursors/correlates in pedigrees of arbitrary size and complexity. For the qualitative disease outcome, a continuous underlying liability distribution is assumed from which disease is determined by a threshold process. This procedure can assess whether correlations between P3 amplitude and alcoholism stem from shared genetic influences. P3 amplitude at all leads showed negative genetic correlations with alcoholism, which indicated the presence of pleiotropic loci that reduce P3 and increase the liability to the disease. Environmental correlations were not significantly different from zero. Genetic correlations were similar for DSM-IV, ICD-10 and DSM-IIIR diagnosis, but were strongest for DSM-IIIR diagnosis. Genetic correlations were strongest at central and temporal leads (-0.61 to -0.71, $p < 0.01$) and weakest at occipital leads (-0.04, $p > 0.10$). Bivariate linkage analyses were per-

formed jointly that considered the disease (diagnosis of alcoholism) and P3 amplitude recorded at the central (Cz) lead (Williams et al., 1998). The pattern of results was similar between diagnoses, but the strongest evidence for linkage was obtained with DSM-IV. A chromosome 4 region near the aldehyde dehydrogenase gene (LOD = 5.79) strongly influenced liability to alcoholism (p = 5.25X10 −7), with evidence for pleiotropic effects on P3 (p = 0.002). A region on 6q (LOD = 3.49) had a strong influence on P3 (p = 0.00004), with evidence for weaker pleiotropic effects on alcoholism (p = 0.004). Bivariate analyses of these P3 findings and diagnosis indicate a dramatic improvement in the power to detect and localize genes jointly that influence these phenotypes.

BEHAVIORAL DISINHIBITION

It should be noted that disinhibitory behaviors such as impulsivity, conduct disorder, and failure to conform to social norms with respect to lawful behavior, are commonly noted as externalizing traits in several clinical conditions (Gorenstein and Newman, 1980). Several genetic studies have demonstrated that alcohol dependence and substance abuse are often comorbid with externalizing traits in children (Weinberg et al., 1998) as well as adults (Wilens et al., 1994). Moreover, the low P3 is not only characteristic of abstinent alcoholics (Branchey et al., 1988; Pfefferbaum et al., 1987, 1991; Porjesz et al., 1980, 1987a, 1987b) and offspring of alcoholics (Bauer et al., 1994; Begleiter et al., 1984, 1987; Benegal et al., 1995; Berman et al., 1993; Hesselbrock et al., 1993; Hill and Steinhauer, 1993; O'Connor et al., 1986, 1987; Porjesz and Begleiter, 1990; Ramachandran et al., 1996; van der Stelt et al., 1998; Whipple et al., 1991), but is also present in other disinhibitory conditions such as substance abuse (Bauer, 1997; Brigham et al., 1997; Herning and King, 1996), antisocial personality (Bauer et al., 1994; Klorman, 1991; O'Connor et al., 1994), and attention deficit hyperactivity disorder (Herning and King, 1996). A number of authors have provided compelling evidence for the presence of externalizing psychopathology in alcoholics and offspring at high risk to develop alcohol dependence (Conrod et al., 1997; Finn et al., 1994; Iacono, 1998; McGue, 1995; McGue et al., 1997; Peterson et al., 1992; Pihl and Bruce, 1995; Pihl et al., 1990; Regier et al., 1990; Sher, 1991; Sher and Trull, 1994; Zucker and Gomberg, 1986).

PHYSICAL DEPENDENCE/CNS HYPEREXCITABILITY

While the diagnosis of alcoholism includes a variety of signs and symptoms, it is important to note that for most nosological systems, the cardinal set of symptoms typically feature the presence of alcohol dependence. Dependence involves a continuum of symptoms most objectively assessed by its endpoint, withdrawal symptoms. Physical dependence develops when the central nervous system becomes physiologically adapted to ethanol, with withdrawal symptoms that appear when a decline in concentration of alcohol occurs. In the absence of alcohol, physical dependence develops and is manifested by an increase in central nervous system hyperexcitability. Symptoms of withdrawal hyperexcitability include tremor, nausea, fever, tachycardia, tinnitus, muscle cramps, diaphoresis, seizures, hallucinations, delirium tremens, etc. These withdrawal symptoms figure in a critical manner into the construct of the "alcohol dependence syndrome" (Edwards and Hadgson, 1981) and continue to be central to various diagnostic classifications (World Health Organization, 1993). The onset of the alcohol withdrawal syndrome is typically gradual, and appears within hours of cessation of alcohol consumption. It has been assumed that chronic alcohol intake causes significant alterations in various brain systems which act to compensate for chronic CNS depression. After cessation of alcohol intake, there is an overcorrection of these deleterious effects that lead to withdrawal symptoms. The resultant effect is a rebound neuronal hyperexcitability that follows the prolonged depression of neural activity caused by chronic alcohol intake.

Several years ago, we (Begleiter et al., 1974) conducted a study in alcoholic individuals to determine the effects of alcohol withdrawal on brain hyperexcitability. Specifically, we measured the recovery function of somatosensory evoked potentials 10 hr after the last drink, during 3 days of baseline, 4 consecutive days of alcoholization, and for 4 days subsequent to withdrawal from alcohol. We observed a progressive increase in brain excitability starting with the intoxication period and reaching asymptote with the first day of total alcohol withdrawal. We have reported a similar phenomenon in a series of experiments conducted in rats. Begleiter and Coltrera (1975) noted increased CNS excitability in rats 24 hr after the last dose of ethanol. Porjesz et al., (1976) reported that the neuroelectric responses of rats previously exposed to alcohol were significantly different from those recorded from naïve animals. In a study in monkeys, we demonstrated (Begleiter et al., 1980) that chronic alcohol intake results in CNS changes which seem to be specific and persist for a relatively long period of time. These data indicated a latent neural hyperexcitability which we labelled as the "protracted subacute postwithdrawal syndrome." It is important to note that this protracted subacute postwithdrawal syndrome is not readily obvious clinically, but may be observed with the use of sensitive neurophysiological techniques. We postulated that the protracted subacute postwithdrawal syndrome might possibly contribute to an increased risk of resuming alcohol consumption. This hypothesis was supported by another study from our laboratory (DeNoble and Begleiter, 1978). We observed that monkeys previously exposed to alcohol self-administered significantly more alcohol during the first 2 alcohol test days, 4 months after the initial alcohol exposure.

Together, these data indicate that exposure to alcohol

leads to CNS hyperexcitability during withdrawal from alcohol. This CNS hyperexcitability persists in a subclinical form, and may possibly cause the resumption of alcohol intake in organisms previously exposed to alcohol. We hypothesize that CNS hyperexcitability is not only observed during the development of physical dependence and in the presence of alcohol withdrawal, but that genetic susceptibility is manifested as hyperexcitability that facilitates the development of alcohol dependence and exacerbates its consequences.

P3 AS AN ENDOPHENOTYPE

As detailed in previous sections, the low voltage P3 is not only characteristic of abstinent alcoholics (Pfefferbaum et al., 1987, 1991; Porjesz et al., 1980, 1987a, 1987b), offspring of alcoholics (Bauer et al., 1994; Begleiter et al., 1984, 1987; Benegal et al., 1995; Berman et al., 1993; Hesselbrock et al., 1993; Hill and Steinhauer, 1993; O'Connor et al., 1986, 1987; Porjesz and Begleiter, 1990; Ramachandran et al., 1996; van der Stelt et al., 1998; Whipple et al., 1991), and some relatives of alcohol dependent individuals (Porjesz et al., 1998), but is also present in children and young adults with disinhibitory conditions (Bauer, 1997; Brigham et al., 1997; Herning and King, 1996; Klorman, 1991) who may be at risk for developing alcoholism. The presence of a low P3 voltage of the ERP in affected and nonaffected members of a family represents a unique feature which provides a powerful endophenotype. This striking neuroelectric finding has been commonly observed by the majority of laboratories throughout the world, and thus at present offers the most optimal endophenotype.

In a recent elegant epidemiological study, Carlson et al. (1999) examined ERPs in 17-year-old individuals sampled from the community. They recorded P3 from several hundred individuals, and then identified statistically a group of subjects with very low P3, and another group at the other end of the distribution with high P3. Subsequently, they noted that the group with low P3 contained significantly more subjects with alcohol and nicotine dependence and illicit drug abuse than the group with high voltage P3. Moreover, the group with low P3 manifested a significantly higher incidence of externalizing disorders than the high P3 group. Together, the aforementioned studies strongly suggest that individuals with various disinhibitory clinical conditions such as alcoholism, as well as their relatives and individuals at risk, typically manifest a low voltage P3. Individuals in the general population with a low P3 manifest a significantly higher incidence of disinhibitory traits and conditions compared to those with a high P3.

It is now well established that low voltage P3 is characteristically observed in alcoholics, their relatives, and offspring. Moreover, the findings described above indicate that low voltage P3 may also be noted in subjects of the general population. These individuals appear to be susceptible to alcohol dependence or drug abuse. One of the fundamental questions related to the presence of low voltage P3 in high risk individuals concerns the potential effect of alcohol in subjects with low P3. In a study on the determinants of P3 amplitude and response to alcohol in Native American mission Indians, Ehlers and colleagues (1998) noted that a low P3 during a placebo condition was predictive of less reduction or an actual increase in P3 amplitude after alcohol challenge. Similar results are being observed by O'Connor and colleagues (personal communication) in Caucasian subjects before and after alcohol clamping.

The use of endophenotypes, such as the P3 voltage of the ERP, is of fundamental use in the search for genes involved in the predisposition toward alcoholism. Furthermore, a review of the literature indicates that low voltage P3 is an index of disinhibition in the central nervous system. This CNS disinhibition may be the central issue in our better understanding of predisposing physiologic features, and may reflect a disequilibrium in CNS interactions.

DISINHIBITION AND ANIMAL STUDIES

Selective breeding of rodents has produced rat lines that manifest high voluntary alcohol consumption (preferrers, P) as well as rat lines with low alcohol intake (nonpreferrers, NP). In recent years, a number of biochemical differences have been correlated with alcohol preference (McBride and Li, 1998). However, few studies have focused on specific behavioral traits that may correlate with alcohol preference. A recent study (Blankenship and Steinmetz, 1998) showed that P rats manifested some difficulty learning an aversive task subsequent to appetitive training in comparison to NP rats. These results suggest that these genetic lines of rodents may differ in behavioral inhibition. The P rats exhibit higher locomotor activity than the NP rats in a novel environment. In other behavioral tasks, the P rats appear more anxious and/or emotional than the NP rats. Ehlers et al. (1999) observed that, similar to human high risk subjects, P rats generated more fast-frequency EEG activity and lower voltage of the P3 component than the NP rats. It should be noted that corticotrophin-releasing factor (CRF) may also have a substantial role to play in alcohol preference. Moreover, recent findings indicate that neuropeptide Y (NPY) may play a major role in seizure modulation (hyperexcitability). Electrophysiological and pharmacological studies have demonstrated that NPY modulates excitatory synaptic transmission and seizure activity. The central administration of NPY in low concentrations is known to produce anxiolysis and suppression of locomotor activity, an outcome similar to that of ethanol. These interesting animal findings are quite consistent with human studies, and demonstrate that rodent lines bred for alcohol preference appear to manifest disinhibition/CNS hyperexcitability.

CNS HOMEOSTASIS BETWEEN EXCITATION AND INHIBITION

The functional relationship between inhibitory and excitatory networks in the brain, as well as the constant modulation of network dynamics by neurotransmitters, neuromodulators, and peptides, are critical for our understanding of homeostasis in the CNS. This CNS homeostasis is responsible for a stable affective state as well as complex cognitive processes. Various neurotransmitters interact with different receptors whose activation can produce a variety of effects on the excitability of specific groups of neurons. It is now well established that gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter. Indeed, one important regulator of recurrent excitation is feedback inhibition provided by the GABAergic interneurons, which receive excitation from pyramidal neurons. It has been conjectured that hippocampal inhibitory circuits are particularly active when the stimulation intensity exceeds a specific threshold level. Sustained activation of these inhibitory networks could result in stimulation of autoreceptors located on the presynaptic neurons. One role of the autoreceptors is to reduce the level of GABA released by the presynaptic cells. A reduced GABA response would naturally result in less inhibition of postsynaptic neurons. Despite the lack of direct evidence linking GABA and P3, it is now well-established that catecholaminergic activity mediates GABA and the resultant inhibitory postsynaptic potentials (Marczynski, 1978).

For cortical homeostasis to remain stable, a delicate balance between excitation and inhibition must be maintained; there needs to be sufficient recurrent excitation to maintain selectivity, and enough recurrent inhibition to prevent excessive excitation. This excessive excitation leads to an instability of the CNS. It should be noted that GABA receptors are sensitive to alcohol (Harris and Allan, 1987). Recent imaging studies have demonstrated significantly reduced levels of GABA-benzodiazepene receptors in alcohol dependent individuals (Lingford-Hughes et al., 1998). Another Positron Emission Tomography (PET) study suggested that alcohol dependence is associated with changes in neurons that contained $GABA_A$-benzodiazepine (BZD) receptors in the superior medial regions of the frontal lobes (Gilman et al., 1996). Two additional studies from Yale support the above findings. In one study, the investigators observed alterations of BZD receptors in type II alcoholics (Abi-Dargham et al., 1998), whereas in another study, the authors found reduced cortical GABA levels in alcohol dependent subjects (Behar et al., 1999). Together, these imaging studies certainly support the role of GABA in alcohol dependent individuals. In addition, a recent PET study from our group that investigated individuals at risk for developing alcoholism provides further evidence of a deficit in the GABA-BZD receptor system (Volkow et al., 1995).

Glutamate is the major excitatory neurotransmitter in the brain. In the cerebral cortex, extrinsic and intrinsic excitatory glutamatergic pathways terminate on principal glutamatergic neurons and local inhibitory GABAergic interneurons. Activation of these complex pathways results in a sequence of excitatory and inhibitory responses in the principal neurons. It is now well established that fast glutamatergic neurotransmission is mediated by three classes of ionotropic receptors, namely NMDA, AMPA, and kainate receptors. Fast GABAergic transmission is mediated by ionotropic $GABA_A$ receptors. The homeostasis between glutamatergic excitation and GABAergic inhibition during normal synaptic neurotransmission involves primarily AMPA, NMDA, and $GABA_A$ receptors. It has been demonstrated that the NMDA receptors are sensitive to the effects of alcohol (Tsai and Coyle, 1998). Although the critical homeostasis between inhibition and excitation is in large measure mediated by these two representative neurotransmitters, it is important to note that other transmitters such as serotonin, norepinephrine, and dopamine also play a major role in homeostasis. Recent evidence indicates that cholinergic activation may reduce some aspects of intralaminar inhibition, and thus facilitate intracolumnar inhibition (Xiang et al., 1998).

CNS HYPEREXCITABILITY: A PROPOSED MODEL

We suggest that what is inherited in the predisposition to developing alcoholism is a general state of CNS disinhibition/hyperexcitability. Thus, we propose that alcohol dependence reflects a state of general CNS disinhibition/hyperexcitability which temporarily can be alleviated by the use of alcohol. Physical dependence, according to Seevers and Deneau (1963) is viewed as an adaptive process in the CNS representing a specific biologic reaction to a few addictive drugs. Specifically, they define physical dependence as "the state of latent hyperexcitability which develops in the cells of the central nervous system following frequent and prolonged administration of ∞ alcohol." This process becomes manifest subjectively and objectively as specific symptoms and signs, the abstinence syndrome or the withdrawal illness, upon abrupt termination of drug administration. Figure 2 is a brief summary of the proposed model.

As depicted in Fig. 2, the genetic predisposition to develop alcoholism is equated with an initial state of disinhibition/CNS hyperexcitability. This CNS homeostatic imbalance can result in a number of externalizing disorders. For several of these high-risk individuals, the exposure to alcohol provides an initially powerful and immediate normalizing effect. However, this relief is temporary, and requires larger and larger amounts of alcohol that results in the development of tolerance. Chronic consumption leads to physical dependence that results in a neuroadaptive excitatory state that normalizes the sedative/hypnotic effects of ethanol. The initial state of disinhibition/CNS hyperexcitability may facilitate this adaptive change and result in a

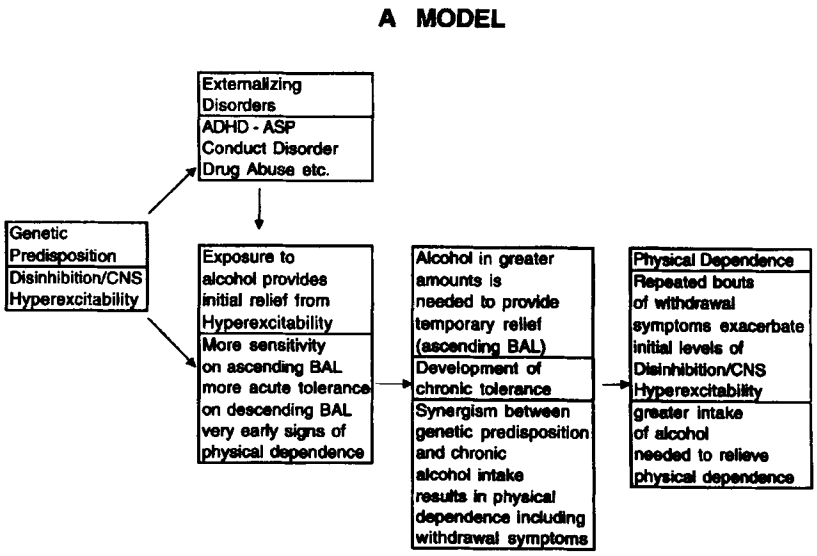

Fig. 2. A schematic chart of the proposed model.

more rapid development of physical dependence, and, in some cases, the manifestation of the withdrawal syndrome.

Several days subsequent to the state of withdrawal, a state of dysphoria is temporarily relieved by alcohol intake. This speculation is in small measure supported by several published experiments that administered alcohol to individuals at high risk (HR) to develop alcoholism. In our laboratory, we have observed that during the ascending phase of the blood alcohol curve, HR subjects manifest an enhanced response to alcohol (Cohen et al., 1993, 1998) compared with low risk (LR) subjects. This may be interpreted as differential sensitivity to the effects of alcohol between HR and LR subjects. It is equally important to note that many studies have noted that during the descending limb of the blood alcohol curve, HR individuals demonstrate a faster recovery to baseline response levels (Cohen et al., 1993, 1998; Ehlers and Schuckit, 1990; Finn et al., 1990; Porjesz and Begleiter, 1992, 1996, 1997; Schuckit, 1985; Schuckit et al., 1988). The aforementioned hypothesis was first suggested as the Differentiator Model (Newlin and Thomson, 1990) which proposes that HR individuals are more sensitive on the ascending limb of the blood alcohol curve and recover more quickly during the descending phase. These results lead to the speculation that HR subjects are more sensitive to the reinforcing properties of alcohol and less sensitive to the deleterious effects of alcohol.

In conclusion, we hypothesize that individuals at genetic risk for the predisposition to develop alcohol dependence manifest a homeostatic imbalance that results in disinhibition/hyperexcitability. This CNS imbalance is akin to the state of hyperexcitability characteristic of alcohol dependence. Dependence first manifests itself not as the acute withdrawal syndrome, but rather as early morning tremors and agitation, which require a drink for immediate relief. The intake of alcohol provides brief, temporary relief typically followed by greater alcohol intake that leads to the reactivation and exacerbation of alcohol dependence. It should be noted that the innate imbalance of excitation/inhibition does not necessarily result in the specific predisposition toward alcohol dependence, but strongly influences the occurrence of one or more adverse disinhibitory conditions. This excessive CNS excitability in individuals at high risk leads, subsequent to chronic exposure to alcohol, to the development of alcohol dependence. Individuals with an imbalance in excitatory/inhibitory homeostatic mechanisms are particularly sensitive to the general pharmacological properties of alcohol as well as other drugs. They seem to be more sensitive to the effects of alcohol on the ascending blood alcohol curve (greater reinforcing properties), and recover more rapidly on the descending limb of the blood alcohol curve (indicative of greater tolerance).

From a genetic perspective, genome-wide searches for genetic loci that influence complex disorders are severely limited by low power. Recently, it has been suggested that the search for quantitative trait loci can result in substantial increases in power with the judicious use of a combination of multiple phenotypes (Allison et al., 1998). Moreover, the substantial increase in power is also a function of the size and direction of the residual correlation among the multiple phenotypes. We recently have demonstrated this phenomenon by conducting a bivariate analysis in the COGA project that used the combination of quantitative and qualitative phenotypes (Williams et al., 1999).

Finally, we must conclude with a strong caveat that the speculative formulation advanced in this paper is not ubiquitous to all alcohol dependent individuals, but only accounts for a certain proportion of etiological factors involved in the genetic predisposition toward the development of alcoholism. Moreover, although predisposing factors render an individual at risk, it is the combination of predisposing and precipitating factors, in the form of alcohol exposure, which ultimately result in the syndrome

of alcohol dependence. The study of predisposing factors in combination with increased knowledge of the pharmacogenetics of alcohol will substantially elucidate our understanding of alcoholism. While the aforementioned model emphasizes a psychobiological diathesis and may be considered speculative, it is our hope that it will enrich our understanding of the role of CNS disinhibition in alcoholism, and thus prove to have heuristic value.

REFERENCES

Abi-Dargham A, Krystal JH, Anjivel S, Scanley E, Zoghbi S, Baldwin RM, Rajeevan N, Seibyl JP, Charney DS, Laruelle M, Innis RB (1998) Alterations of benzodiazepine receptors in type II alcoholics measured with SPECT and (123I)iomazenil. Am J Psychiatry 1551:1550–1555.

Allison DB, Thiel B, Jean PS, Elston RC, Infante MC, Schork NJ (1998) Multiple phenotype modeling in gene-mapping studies of quantitative traits: Power advantages. Am J Hum Genet 63:1190–1201.

Almasy L, Porjesz B, Blangero J, Chorlian DB, O'Connor SJ, Polich J, Kuperman S, Rohrbaugh J, Bauer LO, Reich T, Begleiter H (1998) Heritability of the P300 and N100 components for the even-related brain potential in families with a history of alcoholism. Neuropsychiatric Genet, in press.

Bauer LO (1997) Frontal P300 decrements, childhood conduct disorder, family history, and the prediction of relapse among abstinent cocaine abusers. Drug Alcohol Depend 44:11–10.

Bauer LO, O'Connor SO, Hesselbrock VM (1994) Frontal P300 decrements in antisocial personality disorder. Alcohol Clin Exp Res 18:1300–1305.

Begleiter H, Coltrera M (1975) Evoked potential changes during ethanol withdrawal in rats. Am J Drug Alcohol Abuse 2:263–268.

Begleiter H, DeNoble B, Porjesz B (1980) Protracted brain dysfunction after alcohol withdrawal in monkeys, in Begleiter H (ed): *Biological Effects of Alcohol*. pp 231–250, Plenum, New York.

Begleiter H, Porjesz B, Bihari B, Kissin B (1984) Event-related potentials in boys at risk for alcoholism. Science 225:1493–1496.

Begleiter H, Porjesz B, Rawlings R, Eckardt M (1987) Auditory recovery function and P3 in boys at high risk for alcoholism. Alcohol 4:315–321.

Begleiter H, Porjesz B, Reich T, Edenberg HJ, Goate A, Van Eerdewegh P, Foroud T, Blangero J, Rohrbaugh J, O'Connor SJ, Bauer LO, Kuperman S, Polich J, Litke A, Chorlian DB, Almasy L, Rice J, Hesselbrock V, Li T-K, Conneally PM, Schuckit M, Cloninger R, Nurnberger J Jr, Crowe R, Bloom FE (1998) Quantitative trait loci analysis of human event-related brain potentials: P3 voltage. Electroencephalogr Clin Neurophysiol 108:244–250.

Begleiter H, Porjesz B, Yerre-Grubstein C (1974) Excitability cycle of somatosensory evoked potentials during experimental alcoholization and withdrawal. Psychopharmacologia 37:15–21.

Behar KL, Rothman DOL, Petersen KF, Hooten M, Namanworth S, Delaney R, Petroff OAC, Shulman GI, Navarro V, Petrakis IL, Charney DS, Krystal JH (1999) Preliminary evidence of reduced cortical GABA levels in localized 1H NMR spectra of alcohol dependent and hepatic encephalopathy patients. Am J Psychiatry, 156:952–954.

Benegal V, Jain S, Subbukrishna DK, Channabasavanna SM (1995) P300 amplitudes vary inversely with continuum of risk in first degree male relatives of alcoholics. Psychiatr Genet 5:1–8.

Berman MS, Whipple SC, Fitch RJ, Noble EP (1993) P3 in young boys as a predictor of adolescents' substance abuse. Alcohol 10:69–76.

Birbaumer N, Elbert T, Canavan A, Rockstroh B (1990) Slow potentials of the cerebral cortex and behavior. Physiol Rev 70:1–41.

Blangero J, Almasy L (1996) SOLAR: Sequential Oligogentic Linkage Analysis routines. Technical Notes No. 6. San Antonio, TX, Population Genetics Laboratory, Southwest Foundation for Biomedical Research.

Blankenship MR, Finn PR, Steinmetz JE (1998) A characterization of approach and avoidance learning in alcohol-preferring and alcohol-nonpreferring rats. Alcohol Clin Exp Res 22:1227–1233.

Branchey M, Buydens-Branchey L, Lieber C (1988) P3 in alcoholics with disordered regulation of aggression. Psychiatry Res 1:49–58.

Brigham J, Moss HB, Murrelle EL, Kirisci L, Spinelli JS (1997) Event-related potential negative shift in sons of polysubstance-and alcohol-use dosorder fathers. Psychiatry Res 73:133–146.

Carlson SR, Katsanis J, Iacono WG, Mertz AK (1998) Substance dependence and externalizing psychopathology in adolescent boys with small, average, or large P300 event-related potential amplitude. Psychophysiology, in press.

Cohen HL, Porjesz B, Begleiter H (1993) The effects of ethanol on EEG activity in males at risk for alcoholism. Electroencephalogr Clin Neurophysiol 86:368–376.

Cohen HL, Porjesz B, Begleiter H, Wang W (1997) Neurophysiological correlates of response production and inhibition in alcoholics 21:1398–1406.

Cohen HL, Porjesz B, Stimus A, Begleiter H (1998) Effects of ethanol on temporal recovery of auditory evoked potentials in individuals at risk for alcoholism. Alcohol Clin Exp Res 22:945–953.

Cohen HL, Wang W, Porjesz B, Begleiter H (1995) Auditory P300 in young alcoholics: Regional response characteristics. Alcohol Clin Exp Res 19:469–475.

Conrod PJ, Petersen JB, Pihl RO (1997) Disinhibited personality and sensitivity to alcohol reinforcement: Independent correlates of drinking behavior in sons of alcoholics. Alcohol Clin Exp Res 21:1320–1332.

Deecke L, Heise B, Kornhuber HH, Lang M, Lang W (1984) Brain potentials associated with voluntary manual tracking, in Karrer R, Cohen J, Tueting P (eds): *Event-Related Potentials*. pp 450–464, Annals of the New York Academy of Sciences, New York.

DeNoble V, Begleiter H (1978) Alcohol self-administration in monkeys: The effects of prior alcohol exposure. Pharmacol Biochem Behav 8:391–397.

Desmedt JE: P300 in serial tasks (1980) An essential postdecision closure mechanism, in Kornhuber HH, Deecke L (eds): *Motivation, Motor and Sensory Processes of the Brain*. pp 682–686, Elsevier, Amsterdam.

Edwards G, Arif A, Hadgson R (1981) Nomenclature and classification of drug- and alcohol-related problems: A WHO Memorandum. Bull World Health Organ 59:225–42.

Ehlers CL, Garcia-Andrade C, Wall TL, Sobel DF, Phillips E (1998) Determinants of P3 amplitude and response to alcohol in Native American Mission Indians. Neuropsychopharmacology 18:282–292.

Ehlers CL, Schuckit MA (1990) Evaluation of EEG alpha activity in sons of alcoholics. Neuropsychopharmacology 4:199–205.

Ehlers CL, Somes C, Li T-K, Lumeng L, Kinkead B, Owens MJ, Nemeroff CB (1999) Neurotensin (NT) studies in alcohol naive preferring, and nonpreferring rats. Neuroscience, in press.

Elbert T, Rockstroh B (1987) Threshold regulation: A key to the understanding of the combined dynamics of EEG and event-related potentials. J Psychophysiol 1:314–31.

Emmerson RY, Dustman RE, Shearer DE, Chamberlin HM (1987) Visually evoked and event related potentials in young abstinent alcoholics. Alcohol 4:241–248.

Finn PR, Kessler DN, Hussong AM (1994) Risk for alcoholism and classical conditioning to signals for punishment: Evidence for a weak behavioral inhibition system? J Abnorm Psychol 103:293–301.

Finn PR, Zeitouni NC, Pihl RO (1990) Effects of alcohol on psychophysiological hyperreactivity to nonaversive and aversive stimuli in men at high risk for alcoholism. J Abnorm Psychol 99:79–85.

Gilman S, Koeppe RA, Adams K, Johnson-Greene D, Junck L, Kluin KJ, Brunberg J, Martorello S, Lohman M (1996) Positron emission tomographic studies of cerebral benzodiazepine-receptor binding in chronic alcoholics. Ann Neurol 40:163–171.

Gorenstein EE, Newman JP (1980) Disinhibitory psychopathology: A new prospective and a model for research. Psychol Rev 87:301–315.

Gottesman I, Shields J (1972) *Schizophrenia and Genetics: A Twin Study Vantage Point*. Academic Press, New York.

Halgren E, Stapleton JM, Smith M, Altafullah I (1986) Generators of the human scalp P3(s), in Cracco RQ, Bodis-Wollner I (eds): *Evoked Potentials*. pp 269–286, Alan Liss, New York.

Harris RA, Allan AM (1987) Involvement of neuronal chloride channels in ethanol intoxication tolerance and dependence, in Galanter M (ed): *Recent Developments in Alcoholism*. pp 313–325, Plenum, New York.

Herning RI, King DE (1996) EEG and evoked potentials alterations in cocaine-dependent individuals. NIDA Res Monogr 163:203–223.

Hesselbrock VM (1995) The genetic epidemiology of alcoholism, in Begleiter H, Kissin B (eds): *Alcohol and Alcoholism: Volume 1. The Genetics of Alcoholism*. pp 17–39, Oxford University Press, New York.

Hesselbrock VM, Bauer LO, O'Connor SJ, Gillen R (1993) Reduced P300 amplitude in relation to family history of alcoholism and antisocial personality disorder among young men at risk for alcoholism. Alcohol (Suppl) 2:95–100.

Hill SY, Steinhauer SR (1993) Assessment of prepubertal and postpubertal boys and girls at risk for developing alcoholism with P300 from a visual discrimination task. J Stud Alcohol 54:350–358.

Hill SY, Steinhauer S, Locke J (1995) Event-related potentials in alcoholic men, their high-risk male relatives, and low-risk male controls. Alcohol Clin Exp Res 19:567–576.

Iacono WG (1998) Identifying psychophysiological risk for psychopathology: Examples from substance abuse and schizophrenia research. Psychophysiology 35:621–637.

Katsanis J, Iacono WG, McGue MK, Carlson SR (1997) P300 event-related potential heritability in monozygotic and dizygotic twins. Psychophysiology 34:47–58.

Klorman R (1991) Cognitive event-related potentials in attention deficit disorder. Learning Disabilities 24:130–40.

Knight RT, Scabini D, Wood DL, Clayworth CC (1989) Contributions of temporal-parietal junction to the human auditory P3. Brain Res 502: 109–116.

Lingford-Hughes AR, Acton PD, Gacinovic S, Suckling J, Busatto GF, Boddington SJA, Bullmore E, Woodruff PW, Costa DC, Pilowsky LS, Elle PJ, Marshall EJ, Kerwin RW (1998) Reduced levels of GABA-benzodiazepine receptor in alcohol dependency in the absence of grey matter atrophy. Br J Psychiatry 173:116–122.

Lutzenberger W, Schandry R, Birbaumer N (1978) Habituation of the components of the AEP to stimuli of different intensities, in Kimmel HD, van Olst EH, Orlebeke JF (eds): *The Orienting Reflex in Humans*. pp 123–128, Erlbaum, Hillsdale, NJ.

Marczynski TJ (1978) Neurochemical mechanisms in the genesis of slow potentials: A review and some clinical implications, in Otto DA (ed): *Multidisciplinary Perspectives in Event-Related Brain Potential Research*. Cincinnati, U.S. Environmental Protection Agency, pp 25–35.

McBride WJ, Li T-K (1998) Animal models of alcoholism: Neurobiology of high alcohol-drinking behavior in rodents. Crit Rev Neurobiol 12: 339–369.

McGue M (1995) Mediators and moderators of alcoholism inheritance, in Turner JR, Cardon LR, Hewitt JK (eds): *Behavior Genetic Approaches in Behavioral Medicine*. pp 17–44, Plenum, New York.

McGue M, Slutske W, Taylor J, Iacono WG (1997) Personality and substance use disorders: I. Effects of gender and alcoholism subtype. Alcohol Clin Exp Res 21:513–520.

Miller EK, Li L, Desimone RA (1991) A verbal mechanism for working and recognition memory in inferior temporal cortex. Neuroscience Abstract 2:1377–1379.

Newlin DB, Thomson JB (1990) Alcohol challenge with sons of alcoholics: A critical review and analysis. Psychol Bull 108:383–402.

O'Connor SJ, Bauer L, Tasman A, Hesselbrock V (1994) Reduced P3 amplitudes are associated with both a family history of alcoholism and antisocial personality disorder. Prog Neuropsychopharmacol Biol Psychiatry 18:1307–1321.

O'Connor SJ, Hesselbrock V, Tasman A (1986) Correlates of increased risk for alcoholism in young men. Prog Neuropsychopharmacol Biol Psychiatry 10:211–218.

O'Connor SJ, Hesselbrock V, Tasman A, DePalma N (1987) P3 amplitudes in two distinct tasks are decreased in young men with a history of paternal alcoholism. Alcohol 4:323–330.

Parsons OA, Sinha R, Williams HL (1990) Relationships between neuropsychological test performance and event-related potentials in alcoholic and nonalcoholic samples. Alcohol Clin Exp Res 14:746–755.

Patterson BW, Williams HL, McLean GA, Smith LT, Schaeffer KW (1987) Alcoholism and family history of alcoholism: Effects on visual and auditory event-related potentials. Alcohol 4:265–274.

Peterson JB, Finn P, Pihl RO (1992) Cognitive dysfunction and the inherited predisposition to alcoholism. J Stud Alcohol 53:154–160.

Pfefferbaum A, Ford JM, White PM, Mathalon D (1991) Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. Alcohol Clin Exp Res 15:839–850.

Pfefferbaum A, Rosenbloom M, Ford JM (1987) Late event-related potential changes in alcoholics. Alcohol 4:275–281.

Pihl RO, Bruce KR (1995) Cognitive impairments in children of alcoholics. Alcohol Health Res World 19:142–147.

Pihl RO, Peterson J, Finn PR (1990) Inherited predisposition to alcoholism: Characteristics of sons of male alcoholics. Abnormal Psychology 99:291–301.

Polich J, Bloom FE (1988) Event-related potentials in individuals at high and low risk for developing alcoholism: Failure to replicate. Alcohol Clin Exp Res 12:368–373.

Polich J, Haier RJ, Buchsbaum M, Bloom FE (1988) Assessment of young men at risk for alcoholism with P300 from a visual discrimination task. J Stud Alcohol 49:186–190.

Polich J, Pollock VE, Bloom FE (1994) Meta-analysis of P300 amplitude from males at risk for alcoholism. Psychol Bull 115:55–73.

Porjesz B, Begleiter H (1998) Genetic basis of event-related potentials and their relationship to alcoholism and alcohol use. Clin Neurophysiol 15:44–57.

Porjesz B, Begleiter H (1997) Event- related potentials in COA'S. Alcohol Health Res World 21:236–240.

Porjesz B, Begleiter H (1996) Effects of alcohol on electrophysiological activity of the brain, in Begleiter H, Kissin B (eds): *Alcohol and Alcoholism: Volume 2. The Pharmacology of Alcohol and Alcohol Dependence*. pp 207–247, Oxford University Press, New York.

Porjesz B, Begleiter H (1995) Event-related potentials and cognitive function in alcoholism. Alcohol Health Res World 19:108–112.

Porjesz B, Begleiter H (1992) The effects of alcohol in cognitive event-related potentials in subjects at risk for alcoholism. Poster presented at Genetics and Alcohol Related Diseases June, Bordeaux, France.

Porjesz B, Begleiter H (1990) Event-related potentials in individuals at risk for alcoholism. Alcohol 7:465–469.

Porjesz B, Begleiter H (1985) Human brain electrophysiology and alcoholism, in Tarter R, Thiel DV (eds): *Alcohol and the Brain*. pp 139–182, Plenum, New York.

Porjesz B, Begleiter H, Bihari B, Kissin B (1987a) Event-related brain potentials to high incentive stimuli in abstinent alcoholics. Alcohol 4:283–287.

Porjesz B, Begleiter H, Bihari B, Kissin B (1987b) The N2 component of the event-related brain potential in abstinent alcoholics. Electroencephalogr Clin Neurophysiol 66:121–131.

Porjesz B, Begleiter H, Garozzo R (1980) Visual evoked potential correlates of information processing deficits in chronic alcoholics, in Begleiter H (ed): *Biological Effects of Alcohol*. pp 603–623, Plenum, New York.

Porjesz B, Begleiter H, Hurowitz S (1976) Brain excitability subsequent to alcohol withdrawal in rats, in Ford H, Clouets DH (eds): *Tissue Responses to Addictive Substances*. pp 461–469, Spectrum, New York.

Porjesz B, Begleiter H, Reich T, Van Eerdewegh P, Edenberg HJ, Foroud T, Goate A, Rice J, Litke A, Chorlian D, Blangero J, Stimus AT, Sorbell J, Bauer LO, Kuperman S, O'Connor SJ, Rohrbaugh J (1998) Amplitude of visual P3 event-related potential as a phenotypic marker for a predisposition to alcoholism: Preliminary results from the COGA project. Alcohol Clin Exp Res 22:1317–1323.

Ramachandran G, Porjesz B, Begleiter H, Litke A (1996) A simple auditory oddball task in young adult males at high risk for alcoholism. Alcohol Clin Exp Res 20:9–15.

Regier DA, Farmer M, Rae D, Locke B, Keith S, Judd L, Goodwin FK (1990) Comorbidity of mental disorders with alcohol and other drug abuse. JAMA 64:2511–2518.

Roberts LE, Rau H, Lutzenberger W, Birbaumer N (1994) Mapping P300 waves onto inhibition: Go/no-go discrimination. Electroencephalogr Clin Neurophysiol 92:44–55.

Rockstroh B, Elbert T, Birbaumer N, Canavan A, Lutzenberger W (1989) *Slow Cotrical Potentials and Behaviour*. Baltimore, Urban & Schwarzenberg.

Rockstroh B, Muller M, Cohen R, Elbert T (1992) Probing the functional brain state during P300-evocation. J Psychophysiol 6:175–184.

Schuckit MA (1985) Ethanol induced changes in body sway in men at high alcoholism risk. Arch Gen Psychiatry 42:375–379.

Schuckit MA, Gold EO, Croot K, Finn P, Polich J (1988) P300 latency after ethanol ingestion in sons of alcoholics and controls. Biol Psychiatry 24:310–315.

Seevers MH, Deneau GA (1963) Physiological aspects of tolerance and physical dependence, in Rost WS, Hoffman FG (eds): *Physiological Pharmacology*. pp 565–640, Academic Press, New York.

Sher KJ 1991 (1991) *Children of Alcoholics: A Critical Appraisal of Theory and Research*. University of Chicago Press, Chicago.

Sher KJ, Trull TJ (1994) Personality and disinhibitory psychopathology: Alcoholism and antisocial personality disorder. Abnormal Psychology 103:92–102.

Smith ME, Halgren E, Sokolik M, Baudena P, Musolino A, Liegeois-Chauvel C, Chauvel P (1990) The intracranial topography of the P3 event-related potential elicited during auditory oddball. Electroencephalogr Clin Neurophysiol 76:235–248.

Tsai G, Coyle JT (1998) The role of glutamatergic neurotransmission in the pathophysiology of alcoholism. Ann Rev Med 49:173–184.

van Beijsterveldt T (1996) *The Genetics of Electrophysiological Indices of Brain Activity: An EEG Study in Adolescent Twins*. Universiteit Van Amsterdam, Amsterdam.

van der Stelt O, Geesken R, Gunning WB, Snel J, Kok A (1998) P3 scalp topography to target and novel visual stimuli in children of alcoholics. Alcohol 15:119–136.

Velasco M, Velasco F, Velasco AL, Almanza X, Olivera A (1986) Subcortical correlates of the P300 potential complex in man to auditory stimuli. Electroencephalogr Clin Neurophysiol 64:199–210.

Volkow ND, Wang GJ, Begleiter H, Hitzemann R, Pappas N, Burr G, Pascani K, Wong C, Fowler JS, Wolf AP (1995) Regional brain metabolic response to Lorazepam in subjects at risk for alcoholism. Alcohol Clin Exp Res 19:510–516.

Weinberg NZ, Rahdert E, Colliver JD, Glantz MD (1998) Adolescent substance abuse: A review of the past 10 years. J Am Acad Child Adolesc Psychiatry 37:252–261.

Whipple SC, Berman SM, Noble EP (1991) Event-related potentials in alcoholic fathers and their sons. Alcohol 8:321–327.

Whipple SC, Parker ES, Nobel EP (1988) An atypical neurocognitive profile in alcoholic fathers and their sons. J Stud Alcohol 49:240–244.

Wilens TE, Biederman J, Spencer TJ, Frances RJ (1994) Comorbidity of attention-deficit hyperactivity and psychoactive substance use disorders. Hospital & Community Psychiatry 45:421–435.

Williams JT, Begleiter H, Porjesz B, Reich T, Goate A, Van Eerdewejh P, Foroud T, Edenberg HJ, Almasy L, Blanjero J (1999) Joint multipoint linkage analysis of multivariate quantitative and qualitative traits. II. Alcoholism and event-related potentials. Am J Hum Genet, in press.

Woodward SH, Brown WS, Marsh JT, Dawson ME (1991) Probing the time-course of the auditory oddball P3 with secondary reaction time. Psychophysiology 28:609–618.

World Health Organization (1993) International Classification for Disease (ed 10). Geneva, World Health Organization.

Xiang Z, Huguenard JR, Prince DA (1998) Cholinergic switching within neocortical inhibitory networks. Science 281:985–988.

Yingling CD, Hosobuchi Y (1984) A subcortical correlate of P300 in man. Electroencephalogr Clin Neurophysiol 59:72–76.

Zucker RA, Gomberg ESL (1986) Etiology of alcoholism reconsidered: The case for a biopsychosocial process. Am Psychol 41:783–793.