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Brain Electrophysiology in Subjects at Risk for Alcoholism

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Recent advances in brain imaging have provided unprecedented spatial resolution concerning the neural loci involved in information processing. However, imaging techniques such as computed axial tomography (CAT scan), magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) cannot provide the temporal resolution necessary to understand the dynamic properties of information processing in the human brain.

At present, scalp-recorded event-related potentials (ERPs) provide the only available window to the neurophysiological transactions of the human brain as it processes information on a millisecond to millisecond basis. These powerful ERP techniques occupy the interface between cellular neurobiology and the behavioral or cognitive sciences.

The quantitative measurement of salient features extracted from the ERP reflect aspects of brain function related to sensory, perceptual, and cognitive processes and the structural and functional integrity of various neural systems. The ERP techniques are unique in assessing level of brain function in ways that permit the simultaneous observation of neural events and behavior. These ERP techniques typically require the subject to be actively engaged in a task. An ERP consists of early components related to sensory aspects of stimulation, and later components sensitive to more subjective aspects of cognition. While the early components are obligatory exogenous responses to the physical characteristics of stimulus, the late components reflect endogenous events, and are responsive to internal processing demands.

For the past two decades we have used encephalographic (EEG) and ERP techniques to assess CNS anomalies in chronic alcoholic patients (for review, see Begleiter & Platz, 1972; Porjesz & Begleiter, 1983, 1985, 1987). CNS anomalies have been observed consistently in abstinent as well as current alcoholics

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and were assumed to reflect the deleterious effects of alcohol abuse. In the last decade a number of compelling studies have indicated that genetics do play a significant role in some forms of alcoholism (Cloninger et al., 1981; Goodwin, 1976; see Chapter 25).

The most impressive studies dealing with the possible role of genetics in alcoholism come from large adoption studies. The adoption method allows the investigator to assess genetic and environmental factors independently. One compares the relationship of nonadopted siblings, adopted siblings, biological parents, and adoptive parents so that genetic and environmental effects may be estimated separately. Indeed, this particular methodological approach yields the most compelling evidence of genetic and environmental effects.

The initial adoption studies were conducted in Denmark by Goodwin and colleagues (1973). They observed that the rate of alcoholism in biological sons of alcoholics reared by adoptive parents was the same as in the probands, supporting a role of genetics in alcoholism. Moreover, they found no identifiable home environmental factors that contributed to the risk for alcoholism.

Another set of adoption studies were conducted in Sweden by Cloninger and his colleagues (Bohman et al., 1981; Cloninger et al., 1981). These investigators collected data on 862 men and 913 women adopted at a very early age. They used a sophisticated cross-fostering analysis with a discriminant function analysis of the background of both the biological and adoptive parents, as correlated with mild, moderate, severe, or no alcohol abuse in the male adoptees. They identified two distinct types of alcoholics labeled Type 1 and Type 2. Type 1 had a mild genetic predisposition that strongly interacted with environmental factors and resulted in either mild or severe alcohol abuse. Type 2 manifested a very high rate of heritability estimated at .90 and was associated with early onset, extensive treatment in the biological fathers, as well as antisocial behavior in the biological fathers. The authors estimated the relative risks to be nine for Type 2 and two for Type 1. A significant interaction between genetics and environment was observed for Type 1 but not for Type 2.

Other adoption studies of alcoholism were carried out by Cadoret and his colleagues at the University of Iowa (Cadoret & Gath, 1978; Cadoret et al., 1980). This group found evidence for a genetic and an environmental factor in alcoholism, but failed to observe gene-environment interactions. This lack of gene-environment interaction may be due to their small sample size.

In sum, sophisticated adoption studies have observed a genetic influence in the development of some forms of alcoholism. This genetic influence does not appear to be direct but is seemingly manifested in the presence of predisposing factors. This predisposition may only be expressed with the presence of precipitating factors in the form of environmental events. To the extent that genetic factors are related to a set of predisposing variables, it should be possible to study these variables in individuals with a family history of alcoholism. The identification of factors predisposing some individuals to develop alcoholism is of paramount importance in gaining a better understanding of the etiology of alcoholism, in development of reliable phenotypic markers for a genetic analysis of large pedigrees, and in formulating rational preventive strategies.

In a typical high-risk study, individuals with a family history of alcoholism who are not alcoholic themselves are matched with individuals without a family

history of alcoholism. Both the high-risk group and the low-risk group are assessed on behavioral, physiological, or biochemical variables in the search for potential trait markers. While a number of psychological, behavioral, and biochemical studies have been conducted in subjects at high risk for alcoholism perhaps the electrophysiological findings using spontaneous EEGs and ERPs are the most interesting.

The resting-state EEG recorded from awake abstinent male alcoholics manifests excessive high-frequency activity (beta) and is deficient in the appropriate production of lower EEG frequency activity, such as alpha (for review, see Begleiter & Platz, 1972). It should be noted that some characteristics of the normal EEG are genetically determined (Propping, 1977; Vogel, 1970; Young et al., 1972). These reliable EEG findings in abstinent alcoholics, coupled with the high heritability of normal EEG characteristics and the population genetics data in alcoholism, suggest that individuals at risk for alcoholism should differ from matched controls. Gabrielli et al. (1982) tested this hypothesis in a sample of 265 Danish children. They selected 27 children of alcoholics and compared them with children of parents without alcohol problems. They noted that male children of alcoholics manifested excessive fast EEG activity compared to male controls. This difference in EEG frequency was only specific to males. The investigators readily acknowledge the lack of control regarding the potential psychiatric classification of either or both parents.

In another study by the same group (Pollock et al., 1983), investigators focused specifically on EEG changes subsequent to a challenge dose of alcohol. High-risk subjects were reported to manifest more slow alpha energy, less fast alpha energy, and a lower mean alpha frequency than did the low-risk subjects. However, the prealcohol EEG findings are quite difficult to understand, as the actual statistical findings of the potential difference between high- and low-risk subjects are not given.

In two recent publications, Ehlers and Schuckit (1990, 1991) recorded the EEG in a population of 21- to 25-year-old family history positive (FHP) and family history negative (FHN) males. In one study (Ehlers & Schuckit, 1991), they observed more energy in the fast alpha band (9-12 Hz) in the FHP than in the FHN subjects. In the other study (Ehlers & Schuckit, 1990), they reported no difference between the two groups (FHP-FHN) in the 12-20 Hz EEG band. However, FHN subjects classified as "moderate" drinkers had significantly more power in the 10-20 Hz band than did those classified as "low" drinkers. This finding was not observed in the FHP subjects. The authors conclude that both genetic factors and drinking history may influence electroencephalographic activity in humans.

A study by Kaplan et al. (1988) examined EEG activity between 2 and 20 Hz. No baseline EEG difference was observed between FHP and FHN subjects. A recent study from our laboratory (Cohen et al., 1991) examined EEG activity in the frequency range between 7.5 and 26 Hz in both FHP and matched FHN subjects. Our findings indicated no difference between FHP and FHN subjects in the EEG frequency range examined, replicating the results of Kaplan et al. (1988), Pollock et al. (1983), and Ehlers & Schuckit (1990).

The fact that most of the EEG studies mentioned above indicate that spontaneous EEG activity does not differentiate between FHP and FHN sub-

jects may be due to a number of factors seldom addressed in the literature. It is important to note that the method of subject ascertainment was different in various studies. The selection criteria used to classify subjects as FHP or FHN were substantially different across laboratories. There were also significant mean age differences in subjects recruited. Furthermore, the dependent variables derived from the spontaneous EEG data were not comparable. Finally, none of the aforementioned EEG studies made an effort to control the mental state of the subjects during EEG recording. Failure to control mentation during EEG studies may well increase the variability of the dependent variables, leading to a spurious lack of statistically significant EEG differences. While studies of spontaneous EEG activity in high-risk and low-risk individuals have yielded rather meager findings, studies of event-related brain potentials (ERPs) in these two populations have resulted in many interesting and compelling results.

The ERP is a sensitive index of the functional integrity of various systems in the brain. ERPs not only reflect sensory processes but they are also useful in indexing neurophysiological concomitants of complex cognitive tasks (Donchin et al., 1978; Hillyard et al., 1978). ERPs can easily be recorded in conjunction with behavior or when no behavioral response is required. They can be recorded to attended and unattended stimuli. ERPs reflect the millisecond-to-millisecond transactions that occur in the brain during information processing.

For the past two decades our laboratory has developed and utilized a variety of ERP methods to assess the integrity of various brain systems in abstinent alcoholics. A number of studies have reported prolonged conduction velocities in the brainstem auditory evoked response (BAER, Begleiter et al., 1981; Chu & Squires, 1980; Chu & Yang, 1987; Chu et al., 1982; Rosenhamer & Silfverskiold, 1980). The increases in transmission time were observed in alcoholics abstinent for a relatively short period of time (3-4 weeks). Improvement in conduction velocity has been observed with prolonged abstinence (Nickel & Ludewig, 1981; Porjesz & Begleiter, 1985).

A number of investigations have also utilized ERPs to assess the functional integrity of higher integrative systems. Target-selection paradigms have been used for recording ERPs in alcoholics in the auditory (Pfefferbaum et al., 1980; Salmay et al., 1980) and visual (Begleiter et al., 1980; Porjesz et al., 1980, 1987a) modalities, as well as bimodally (Patterson et al., 1987; Porjesz & Begleiter, 1979). An information-processing ERP paradigm provides an opportunity to compare neuroelectric and behavioral responses to identical relevant and irrelevant stimuli. Control subjects in our study demonstrated an enhanced N1 component to stimuli in the relevant as opposed to irrelevant modality (Porjesz & Begleiter, 1979). In contrast, alcoholics maintained the same N1 voltage regardless of task relevance.

In other studies we investigated the late positive complex (LPC) of the ERP, which typically contains the P3b component (P3). Specifically, we examined the ability of abstinent alcoholics to differentiate between relevant and irrelevant events and their ability to probability match stimuli in accordance with their frequency of occurrence. We repeatedly observed that P3 amplitudes were low or absent in alcoholic patients to rare target stimuli under conditions optimal for eliciting large P3 voltages. This finding typically differentiates alco-

holics from control subjects and is most striking over the parietal area where P3 amplitude is found to be maximal in control subjects.

The decreased P3 voltages in the ERP observed in our alcoholic patients were obtained in a variety of studies in our laboratory (Begleiter et al., 1980; Porjesz & Begleiter, 1979, 1982; Porjesz et al., 1980, 1987a & b) and have been replicated by other investigators (Emmerson et al., 1987; Patterson et al., 1987; Pfefferbaum et al., 1987). The consistent reductions in the P3 voltage of the ERP were assumed to reflect the neurotoxic effects of alcohol on the CNS of alcoholic patients.

Recent studies in genetic epidemiology indicate that alcoholism is a highly familial disease. Sons of alcoholic fathers are four times more likely to develop alcoholism than sons of nonalcoholic fathers even when they are separated from their biological parents. Because of these striking findings, we have initiated a series of investigations over the past decade to examine the possible presence of neurophysiological anomalies in subjects known to be at risk for alcoholism.

In the first study, Begleiter et al. (1984) tested the hypothesis that deficits in P3 voltage of the ERP may antecede the onset of chronic alcohol abuse, and may be present in boys at high risk for alcoholism. ERPs were recorded from 25 young, never-exposed sons of alcoholic fathers and 25 control boys matched for age, socioeconomic status, and school grade, who had no family history of alcoholism. The experimental paradigm consisted of a complex visual mental rotation task to identify the orientation of a target stimulus. The high-risk group showed a significantly reduced amplitude of the late positive component (P3) of the ERP, similar to results obtained in abstinent alcoholics (Porjesz & Begleiter, 1985); this reduced amplitude was originally presumed to be solely the consequence of alcoholism. These findings are particularly interesting because they were obtained in young, nondrinking sons of alcoholics without administering alcohol.

Using the same experimental paradigm as Begleiter et al. (1984), O'Connor et al. (1986) recorded ERPs in an older (20-25 years of age) group of sons of alcoholic fathers and matched controls. None of the subjects manifested signs of problem drinking. These investigators also observed a significantly reduced amplitude of the P3 component of the ERP in the high-risk men, replicating the findings of Begleiter et al. (1984).

Begleiter et al. (1987a) then used the brainstem auditory evoked response (BAER) to assess the auditory pathway in young boys at high risk for alcoholism. The investigators examined 23 sons of alcoholics (7-13 years old) and 23 control boys matched for age, socioeconomic status, and school grade. No significant difference in the BAER was found between high-risk and low-risk boys. These results suggest that the BAER abnormalities observed in abstinent alcoholics are likely to be the consequence of alcoholism, whereas the P3 deficits seen in both abstinent alcoholics and individuals at high risk for alcoholism may be antecedents of alcoholism.

In order to determine if the P3 findings in high-risk individuals were modality specific, Begleiter et al. (1987b) studied auditory evoked potentials in another group of high- and low-risk boys. The subjects were 23 young boys (7-16

years old) who were sons of alcoholic fathers and 23 control boys without a family history of alcoholism matched for age, school grade, and socioeconomic status. The subjects in this study were carefully interviewed to ascertain that they had had no exposure to alcohol or other illicit drugs. Clinical examination of the fathers of these young sons of alcoholics indicated that they met the criteria for male-limited (type 2) alcoholism as proposed by Cloninger (1987). They came from families in which familial alcoholism occurred only in males, was highly heritable, gave rise to severe early-onset alcoholism with a high rate of recidivism requiring extensive treatment, and was accompanied by the occurrence of petty criminality.

An auditory oddball paradigm was developed in which subjects pressed a button to discriminable infrequent stimuli. While the auditory pitch discrimination was a relatively easy sensory discrimination, the three interstimulus intervals (0.5, 1.0, and 5.0 seconds) randomized in the study increased the temporal uncertainty and thus the difficulty of the task. The results indicated that boys at high risk for alcoholism manifested significantly reduced amplitudes of the P3 component of the ERP. This auditory study indicates that P3 reductions in high-risk males are present in the visual and auditory modalities and thus are not modality specific.

More recently, we replicated our original findings of reduced P3 voltages without the administration of alcohol in an older sample (18-23) of sons of male alcoholics (Porjesz & Begleiter, 1990). The sample consisted of 25 male offspring of carefully diagnosed (DSM-III/RDC) male alcoholics and was selected from high-density alcoholic families (mean number of alcoholic family members = 4). Thus, sons of alcoholic fathers were excluded in cases where alcoholism may have been sporadic. Furthermore, individuals with mothers who abused alcohol before, during, or after pregnancy were excluded. Controls were matched to 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. Family history positive and negative subjects were carefully matched on drinking history, including duration and quantity-frequency information.

We used a visual-spatial paradigm with which we had previously demonstrated that abstinent alcoholics manifested reduced P3 amplitudes. The stimuli consisted of a nontarget (vertical line) and two targets: an easily discriminable target that deviated from vertical by 90 degrees (horizontal line) and a difficult-to-discriminate target that deviated from vertical by only 3 degrees. The subject pressed a button as quickly as possible (RT) to all nonvertical stimuli.

The study indicated that, without alcohol ingestion, P3 amplitude is significantly lower in high-risk subjects compared to controls. This replicates our previous findings (Begleiter et al., 1984, 1987b) of lower voltage P3s in an older sample of high-risk males as well as those of O'Connor et al. (1986, 1987) and Whipple et al. (1988). The largest differences in P3 amplitude between groups occurred to the easy target, to which low-risk subjects manifested extremely high voltages. These results are similar to those we obtained in alcoholics with the same paradigm, where the easy target elicited the greatest significant difference in P3 amplitude between groups (Porjesz et al., 1987a). This P3 amplitude

difference between groups was most apparent at Pz and Cz electrodes in both studies.

Thus, P3 amplitudes are reduced in voltage in older and younger high-risk nonalcoholic males both to easy and difficult discriminations, in visual and auditory modalities, and without the administration of alcohol. As these results have now been replicated in four different laboratories—O'Connor et al. (1986, 1987, unpublished data), Steinhauer et al. (1987), Whipple et al. (1988), and Amass et al. (personal communication)—under different experimental conditions, these results seem to be generalizable. The neurophysiological deficits observed in young male offspring of male-limited alcoholics are intriguing in light of neurochemical deficits found only in male-limited alcoholics and high-risk individuals (Von Knorring et al., 1985).

Other investigators have reported differences in P3 between high-risk and low-risk individuals only after the administration of either alcohol or placebo. Elmasian et al. (1982) studied the P3 component as well as the slow-wave component of the ERP in three separate groups of subjects, each consisting of five matched pairs (five high risk and five low risk); one group served as the placebo group, the second group received a low dose of alcohol, and the third group was administered a high dose of alcohol. The subjects were male college students between 20 and 25 years of age who were primarily social drinkers. The investigators observed a significant decrease in the amplitude of the P3 component in the high-risk compared to the low-risk subjects. However, this finding was only observed after the administration of either alcohol or placebo. The investigators suggest that all subjects expected to receive alcohol; however, only high-risk subjects manifested a specific expectancy for alcohol characterized by an unusual brain event. It is also suggested by the investigators that higher-than-normal alcohol intake in the mothers of high-risk individuals may result in altered brain physiology.

Another study conducted in the same laboratory (Neville & Schmidt, 1985) examined the late positive component of the ERP in young adults at risk for alcoholism and low-risk individuals. This study did not involve the ingestion of alcohol or placebo and therefore eliminated expectancy for alcohol as a potential confounding factor. Moreover, the mothers of all subjects were interviewed to determine their use of alcohol and other drugs. Group differences in the late component of the ERP were observed.

In a subsequent study, Schmidt & Neville (1985) recorded ERPs in high- and low-risk men while they performed a visual language task. All subjects were social drinkers. They found that the amplitude of the N430 component was significantly smaller in men at high risk compared to men at low risk for alcoholism. Moreover, the latency of the N430 was directly related to the amount of alcohol consumed per occasion in the high-risk group. These results imply that neuronal function associated with language processes are affected by family history of alcoholism, and the interaction between family history and alcohol consumed per occasion.

We examined the effects of alcohol on ERPs in high- and low-risk subjects selected carefully, as noted above. All individuals were tested one week apart,

ethanol (0.5 ml/kg), and high dose (0.8 ml/kg)—were randomized across subjects. At this point, we have tested 50 subjects (25 high-risk and 25 low-risk individuals). On each occasion, each subject was tested once before the administration of one of three liquids, and four times subsequent to liquid ingestion: 30, 60, 90, and 120 minutes after ingestion.

In this experiment the subjects were engaged in the visual line paradigm described earlier in this chapter (Porjesz & Begleiter, 1990). It is a P3 paradigm involving easy and difficult line discriminations. We found that, for both the easy and difficult targets, the high-risk subjects produced a P3 voltage that was significantly ($P < 0.01$) lower than that produced by the low-risk subjects both before (Porjesz & Begleiter, 1990) and after ethanol ingestion.

These results of lower P3 voltages obtained in young adult men at high risk for alcoholism replicate our past findings in young boys at high risk for alcoholism (Begleiter et al., 1984, 1987b) as well as the findings by O'Connor et al. (1986, 1987, unpublished data) and Whipple et al. (1988). Taken together, these findings of reduced P3 amplitudes in high-risk males have now been replicated with many different paradigms in different laboratories. This indicates it is not task or modality specific; it can be obtained both under speed and accuracy conditions, with and without alcohol administration, in different age groups.

It is of interest to note that ERPs appear to be quite heritable; they also seem to be rather similar in abstinent alcoholic fathers and their sons (Whipple et al., 1988). The P3 deficits identified in abstinent alcoholics also discriminate between boys at high and low risks for alcoholism. Therefore, we postulate that the ERP deficits identified in high-risk populations may be quite useful as potential phenotypic markers. Such a reliable and sensitive phenotypic marker may be of great utility in conducting a linkage analysis in large family pedigrees.

Taken together, the neurophysiological studies conducted in populations at high risk for alcoholism indicate rather clear differences between high- and low-risk individuals. While many questions remain unanswered, these preliminary findings seem quite intriguing and merit further neurophysiological investigations.

It is becoming critical to understand the significance of the aforementioned neurophysiological findings in populations at high risk for alcoholism. We need to assess the relationship between neuroelectric deficits in sons of alcoholics and subsequent alcohol abuse and alcoholism. The possible predictive value of electrophysiological deficits in young sons of alcoholics can only be assessed by the use of longitudinal studies in which individuals at high and low risk for alcoholism are tested regularly over several years until they pass through the period of maximum risk for alcoholism.

It is well established that alcoholism is not a homogeneous disorder with a unidimensional etiology. A potential biological marker may be present in subjects at high risk for one type of alcoholism but not for other types of alcoholism. In addition, a biological marker for alcoholism is not necessarily specific to this disorder. Indeed, it may be argued that the addictive behaviors represent a set of behaviors optimizing short-term gratification at the expense of long-term deleterious effects. In this context, the addictive behaviors reflect a failure in

behavioral regulation. The failure of self-regulatory systems results in the inability to delay gratification as well as to avoid long-term consequences. Addictive behaviors, including alcoholism, might be interpreted as failures of adaptive self-regulatory processes. Indeed, one may argue that all addictive behaviors represent the natural consequence of behavioral dysregulation. This dysregulation is manifested by a significant deficiency in sensitivity to both exteroceptive and interoceptive stimuli that are critical to self-regulation. Moreover, this insensitivity to external and internal stimuli may be partially under genetic control. It has been argued that internal cue insensitivity is a possible diathesis for self-regulatory difficulties (Tarter et al., 1984). These authors assert that alcoholism is a disorder in the cognitive-physiological integration of information caused by a faulty arousal system. Indeed, alcoholics are well known to manifest problems with impulsivity, socialization, and self-control. The main components of self-regulation, including planning, guiding, and monitoring of one's own behavior, are substantially deficient in all disorders of behavior dysregulation.

It may be conjectured that the neurophysiological markers we have summarized in this chapter reflect behavioral dysregulation. To the extent that this dysregulation involves a set of behaviors common to different adverse outcomes, it may be speculated that alcoholism and other disorders of excess have a genetic predisposition, but may require environmental influences to determine the final pathway for expression of the disorder. Alcoholism may not be a unique biologically determined disease, but may be one of a variety of adverse outcomes shaped by genetically determined predisposing factors and precipitated by environmentally determined factors.

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Cocaine Addiction: Psycho-Neurophysiology, and Treatment

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CLINICAL CHARACTERISTICS OF COCAINE ADDICTION

For the past few years we have been experiencing the largest cocaine epidemic in history. In the United States alone, one to three million abusers are estimated to be in need of treatment (Adams & Kozel, 1986), six times the number of heroin addicts. In the 1880s, 1890s, and 1920s, cocaine use surged, was temporarily considered safe, and declined after its abuse became well known (Freud, 1884; Lewin, 1887; Maier, 1926). In the early and late 1960s, abuse of the similar stimulants, amphetamine and methamphetamine, followed the same pattern (Ellinwood, 1974). In the 1970s, cocaine was considered a relatively safe, nonaddicting euphoriant (Grinspoon & Bakalar, 1980; National Commission on Marijuana and Drug Abuse, 1973). Early descriptions of cocaine dependence were dismissed as exaggerations similar to marijuana reports from earlier eras. No clinical research on cocaine using systematic and objective techniques had been done, and it was assumed that cocaine dependence did not exist. Then in the 1980s cocaine use exploded. Population data show almost a half of Americans now between 18 and 35 years of age have tried cocaine. A powerful route of administration, cocaine smoked as "crack," is now widespread, and it is as addictive as intravenous injection without its stigma or infectious dangers (Gawin & Griffith, 1986a; Grabowski, 1984; Jekel et al., 1986; Siegel, 1982).

Abusers in treatment typically report that two to four years elapse between initial exposure to cocaine and the development of addiction (Kleber, 1985a). This interval delays awareness of adverse effects at the beginning of stimulant epidemics and, combined with reports of apparently controlled initial use, promotes an illusion of cocaine's safety. Early on, the