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Evoked Brain Potentials and Alcoholism

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Introduction

The relative inaccessibility of the living human brain to direct neurobiological scrutiny has made it difficult to examine brain dysfunction in alcoholism. While it has long been apparent that the human brain is very susceptible to both the acute and chronic effects of alcohol, it is only recently, with the development of sophisticated technology, that these effects have been studied *in vivo*. The development of advanced computer technology has made it possible to investigate functional brain deficits in alcoholics with noninvasive evoked brain potential (EP) techniques. These EP techniques permit an examination of more subtle forms of brain damage and/or dysfunction that was heretofore not possible. The event-related potential (ERP) techniques offer a unique approach for assessing level of brain functioning, as they permit the simultaneous observation of electrophysiology and cognition.

An ERP is obtained by recording the time-locked brain electrical activity with a noninvasive scalp electrode following the delivery of a discrete stimulus to any sensory modality (e.g., auditory, visual). Signal-averaging techniques make it possible to extract these time-locked neuroelectric signals (ERPs) from the background random "noise," which is canceled out with these procedures. Depending on stimulation properties and recording sites, these time-locked signals represent activity at neural generators from the peripheral end organ to higher integrative centers of the brain. The quantitative measurement of salient features extracted from ERP recordings provide objective neurophysiological data reflecting various aspects of brain function related to integrative processes, as well as the functional integrity of different neuroanatomical systems. Thus, with the use of these sophisticated neurophysiological techniques, the functional integrity of various systems of the brain (from peripheral end organs to the neocortex) can be assessed.

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ERP techniques have proven to be very useful in indexing electrophysiological concomitants of complex cognitive tasks (Donchin, 1979; Donchin, Ritter, & McCallum, 1978; Hillyard, Picton, & Regan, 1978). They can be recorded in conjunction with behavior, or even when no behavioral response is required, to both attended and unattended stimuli. Thus the ERP techniques are very sensitive indices of the functional integrity of the brain. They differ from the computerized tomography (CT) scan in that they reflect subtle, dynamic, moment-to-moment changes in brain functioning that are elicited while the brain is being challenged, rather than the static, gross brain damage that is apparent on the CT scan. ERP aberrations are often observed in the absence of brain damage as visualized on CT scan.

Evoked Brain Potentials and Alcoholism

EP techniques have provided indices sensitive to the various alcohol effects—namely, alcoholization, tolerance, withdrawal, and long-term brain dysfunction. Alcoholization is characterized by marked depressions in EP amplitude (Bierley, Cannon, Wehl, & Dustman, 1980) and by prolongations in conduction velocities of the brain stem potential (BSP) (Chu, Squires, & Starr, 1978; Squires, Chu, & Starr, 1978a, 1978b). Chronic alcohol intake is accompanied by EP amplitude reductions (Begleiter & Porjesz, 1977; Porjesz, Begleiter, & Hurowitz, 1976) and by BSP delays that are less pronounced when tolerance develops (Chu *et al.*, 1978; Squires *et al.*, 1978a, 1978b; Zilm, Kaplan, & Capell, 1981). These techniques are also very sensitive to withdrawal phenomena, which are characterized by increased EP voltages and extremely shortened BSP latencies, indicative of underlying CNS hyperexcitability (Begleiter & Porjesz, 1977, 1979; Begleiter, DeNoble, & Porjesz, 1980; Chu *et al.*, 1978; Hunter & Walker, 1980; Squires *et al.*, 1978a, 1978b). Finally, long-term abstinence is marked by decreased EP amplitudes (hyporeactivity) and by prolonged BSP latencies and slower conduction velocities (Begleiter, Porjesz, & Chou, 1981; Porjesz & Begleiter, 1983). The duration of these prolonged CNS disturbances and their potential recovery are not yet known. For the last several years in our laboratory, we have undertaken a systematic program of research to assess brain dysfunction in alcoholics with the use of these sensitive EP techniques.

Auditory Brain Stem Potentials

We have recently recorded auditory BSPs from hospitalized alcoholics who were abstinent from alcohol for 1 month (Begleiter *et al.*, 1981). With this technique, it is now possible to investigate subcortical brain functioning with a noninvasive scalp electrode (Jewett, 1970; Jewett & Williston, 1971; Sohmer & Feinmesser, 1967). These "far-field" potentials consist of time-

locked positive waves, each presumed to reflect activity at different sites along the auditory pathway from the auditory nerve through the brain stem (Buchwald & Huang, 1975; Jewett, 1970; Lev & Sohmer, 1972; Starr & Achor, 1975; Starr & Hamilton, 1976; Stockard & Rossiter, 1977). The latencies of each of these peaks, as well as "central conduction time" (the latency of each peak with respect to peak I), are accurate in localizing sites of pathology from the peripheral end organ to the brain stem; the time interval between the peak I and peak V of the inferior colliculus is most often taken as a measure of brain stem transmission time (Fabiani, Sohmer, Tait, Gafni, & Kirati, 1979).

In our study, we found that alcoholic patients manifested significant delays in latencies and central conduction velocities of peaks II–V. These findings are remarkably similar to those reported with acute doses of alcohol in animals (Squires *et al.*, 1978b) and humans (Squires *et al.*, 1978a). Our study provides the first systematic electrophysiological evidence of brain dysfunction at levels other than neocortex in alcoholics without overt clinical signs of neurological damage. The increase in neural transmission time may reflect the process of demyelination, which has long been suspected in alcoholics (Adams, Victor, & Mancall, 1959) and has been observed in rats chronically exposed to alcohol (Moscatelli & Demediuk, 1980). Similar results have recently been reported in neurologically impaired alcoholics (Chu & Squires, 1980; Chu, Squires, & Starr, 1982; Haas & Nickel, 1981; Nickel & Ludewig, 1981; Rosenhamer & Silfverskiold, 1980) and in neurologically intact alcoholics (Cassvan, Rosenberg, & Caliguiri, 1984). The etiology of these auditory BSP delays, and the drinking-history factor(s) (e.g., length of drinking history, amount consumed per sitting, number of withdrawals, nutritional factors, etc.) that result in brain stem aberrations, have not yet been definitively determined. It is even possible that nutritional deficiencies alone produce demyelination and hence the BSP delays. Nutritional deficits are known to lead to demyelinating diseases such as polyneuropathy (Hillman, 1974). At present, we are investigating the relationship between drinking-history and nutritional factors and the magnitude of BSP aberration. Our preliminary data suggest that alcoholics with signs of nutritional deficits and/or polyneuropathy display BSP waveforms that are different from those of other alcoholics. Furthermore, length of drinking history does not seem to correlate with BSP delay; in fact, alcoholics with relatively short histories of heavy drinking (less than 8 years) but evidence of nutritional deficits manifested greater BSP aberrations than alcoholics with long drinking histories (more than 20 years) and no signs of nutritional deficits.

Taken together, these findings suggest that BSP aberrations in alcoholics may be the result of alcohol and/or nutritional factors. The results of animal data (Chu *et al.*, 1978) suggest that other factors besides chronic alcohol exposure are necessary to produce BSP abnormalities, as chronic

alcohol ingestion in the absence of nutritional deficits in laboratory animals is not sufficient to cause BSP delays after withdrawal.

Event-Related Potentials

As noted earlier, another promising neurophysiological approach in assessing brain functioning is the ERP technique. For the past several years, we have systematically examined ERPs in medication-free alcoholics who have been abstinent for approximately 1 month. These ERP techniques require the subject to be engaged in a task (usually information processing). Each task is designed to examine deficits of a particular ERP component. In the ERP literature, these components have been well documented to vary predictably under specific conditions in normal subjects (Donchin *et al.*, 1978; Hillyard *et al.*, 1978).

In one bimodal (visual and auditory) study, we investigated the ability of alcoholics to focus on a relevant stimulus modality and inhibit responding to an irrelevant modality, by examining the N100 component of the ERP (Porjesz & Begleiter, 1979), a component that occurs at a latency of about 100 msec. The N100 component is sensitive to the selection of a relevant or irrelevant stimulus modality in healthy subjects; it is enhanced to all stimuli in a relevant stimulus modality, and reduced to stimuli in irrelevant modalities (Hillyard, Hink, Schwent, & Price, 1973; Hillyard *et al.*, 1978; Picton & Hillyard, 1974). The patients were presented with a sequence of randomized single flashes and clicks, with rarely occurring double flashes and clicks interspersed among them. They were required to "shift attentional sets" by counting either the double flashes or double clicks, or ignoring all stimuli, in an otherwise identical stimulus sequence. ERPs were obtained only to the irrelevant single flashes, which were either in the relevant or irrelevant stimulus modality in a given condition; such frequent single flashes elicit N100 components that are differentially enhanced in the relevant channel (stimulus modality).

The results indicated that abstinent alcoholics manifested abnormally reduced late-component amplitudes (less than 100 msec), but not early-component amplitudes. These findings in abstinent alcoholics are remarkably similar to results obtained when healthy subjects ingested single doses of alcohol (E. G. Lewis, Dustman, & Beck, 1969; Porjesz & Begleiter, 1975; Rhodes, Obitz, & Creel, 1975). This suggests that the neurophysiological brain dysfunction observed in abstinent alcoholics may resemble brain functioning detected in normal persons under the influence of alcohol. Often it is the differential voltage between ERPs obtained to stimuli in relevant and irrelevant channels that is more revealing about the nature of brain functioning than absolute voltages to either relevant or irrelevant stimuli. Consistent with the ERP literature (Hillyard *et al.*, 1973, 1978), control subjects in our study manifested significantly enhanced N100 com-

ponents to stimuli in the relevant as compared to the irrelevant modality; however, alcoholics maintained the same low amplitude of N100, regardless of degree of task relevance. These results suggest that alcoholics may be incapable of appropriate "sensory filtering," as they do not neurophysiologically differentiate between relevant and irrelevant channels.

We have also used the P300 component of the ERP to examine brain dysfunction in alcoholics, with many different experimental paradigms. The P300 component is a large positive deflection that occurs approximately 300–500 msec after the stimulus. It can only be elicited under certain rather specific conditions related to the "subjective significance" of a stimulus—namely, task relevance (Sutton, Tueting, Zubin, & John, 1967), unpredictability (Donchin *et al.*, 1978), and infrequency (Tueting, Sutton, & Zubin, 1971)—as well as by motivational factors (Begleiter, Porjesz, Chou, & Aunon, 1983). The characteristics of P300 are unrelated to stimulus parameters, and can even be elicited in the absence of an expected stimulus (emitted potentials) (Klinke, Fruhstorfer, & Finkenzeller, 1968). In terms of scalp topography, P300 has been found to be maximum over parietal areas; it is bilaterally distributed without apparent hemispheric asymmetry, with similar distributions regardless of the sensory modality of the stimulus (Simson, Vaughan, & Ritter, 1976, 1977a, 1977b).

In one study in our laboratory, we investigated the P300 component with a visual target-selection paradigm (Porjesz, Begleiter, & Garozzo, 1980). The target selection paradigm is most frequently used to elicit a P300 component; it requires the subject to detect a designated rarely occurring target stimulus embedded in a series of frequently occurring nontarget stimuli. ERPs recorded to frequently occurring nontarget stimuli elicit N100 components, but no P300, while rare target stimuli elicit both N100 and P300 components. In our study (Porjesz *et al.*, 1980), the stimuli were geometric shapes. One rare geometric shape (e.g., a triangle) was designated target, and the subject was required to press a button only to that stimulus. Target and nontarget stimuli were alternated every other block, enabling the recording of ERPs to the same stimulus when it was target or nontarget. ERPs were recorded to target (rarely occurring, task-relevant geometric shapes), nontarget (frequently occurring, task-relevant geometric shapes), and novel (rarely occurring, task-irrelevant random shapes) stimuli.

Despite the fact that all stimuli were in the relevant channel, we found that the N100 amplitudes were significantly depressed in alcoholics to all stimuli, to levels comparable to an irrelevant stimulus modality. As in our bimodal study (Porjesz & Begleiter, 1979), this suggests that "sensory-filtering" mechanisms are impaired in chronic alcoholics. Furthermore, we found that P300 amplitudes were significantly reduced or absent in alcoholic patients to rare target stimuli under conditions optimal for eliciting large P300s (Donchin *et al.*, 1978). This finding was most pronounced over parietal areas, where P300 amplitude is maximal at scalp (Ritter, Vaughan,

& Costa, 1968; Simson *et al.*, 1977a, 1977b). Furthermore, while controls manifested differentially enhanced late P300 components to target stimuli, alcoholics manifested identical low-amplitude P300 waves with the same P300 latencies, regardless of whether a stimulus was target or nontarget. Thus, the major ERP aberrations manifested by alcoholics are the lack of differentiation between their responses to relevant and irrelevant inputs, and the low voltages of their event-related activity. This seems to suggest underlying brain dysfunction that impairs "sensory-filtering" and "probability-matching" processes.

Despite its maximal amplitude over parietal areas at the scalp, recent evidence suggests that the neural origins of P300 may be subcortical and may implicate the amygdala and hippocampus. One recent study investigating the neural origins of P300 with implanted electrodes in humans reported that P300 was maximum at subcortical loci (Wood, Allison, Goff, Williamson, & Spencer, 1980). Similarly, Halgren *et al.* (1980) have recently recorded large late potentials from the limbic system with implanted electrodes in humans. They postulate that P300 may be generated in the hippocampus or the amygdala.

Thus, our findings that alcoholics manifest low-voltage or even absent P300 components under conditions designed to elicit maximum P300 component amplitudes may be indicative of hippocampal deficits. While these results do not rule out the contributions of cortical sites, they emphasize the important role of limbic structures in generating the P300 component. The involvement of the hippocampus in chronic alcohol intake in the absence of malnutrition has been recently demonstrated in neuropathological and neurophysiological studies in animals (Begleiter, DeNoble, & Porjesz, 1980; Riley & Walker, 1978; Walker, Barnes, Zornetzer, Hunter, & Kubanis, 1980; Walker, Hunter, & Abraham, 1981). Long-term ethanol consumption has been found to result in the loss of dendritic spines in mouse (Riley & Walker, 1978) and rat (Walker *et al.*, 1980) hippocampus. In our laboratory, we have also demonstrated a hippocampal susceptibility to both acute and chronic alcohol effects with evoked potentials recorded from monkey hippocampus (Begleiter, DeNoble, & Porjesz, 1980).

We were interested in determining the relationship between electrophysiological deficits and structural deficits assessed with CT scan in alcoholics (Begleiter, Porjęsz, & Tenner, 1980). We selected two groups of alcoholics who had been subjected to CT scans following 1 month of abstinence: namely, those manifesting a high degree of widened cortical sulci (Pos-CT) and those without any evidence of widened cortical sulci (Neg-CT). Patients in the two groups did not differ with regard to age, education, and drinking history (duration and amount). ERPs were recorded on the same day as the CT scan and involved the same P300 paradigm previously described (Porjesz *et al.*, 1980). Alcoholics with enlarged cortical sulci (Pos-CT) had significantly reduced (or absent) P300 amplitudes to target stimuli as com-

pared to alcoholics without signs of enlarged cortical sulci (Neg-CT); however, both groups manifested smaller P300s to targets than did control subjects. Furthermore, both groups of alcoholics displayed similar P300 components to all categories of stimuli, regardless of task relevance.

As alcoholics without signs of widened cortical sulci also manifested diminished P300 amplitudes when compared to healthy nonalcoholics, neocortical shrinkage alone cannot explain these P300 reductions. These findings suggest that chronic alcohol abuse not only results in changes in the neocortex, but may also involve electrophysiological aberrations indicative of other brain (e.g., limbic system) deficits. Often the neocortical deficits in chronic alcoholics are emphasized while subcortical aberrations are overlooked. Our results suggest that alcoholics manifesting observable widened cortical sulci on CT scan are more likely to manifest hippocampal deficits as well. This perhaps lends support to the hypothesis that alcohol produces diffuse brain damage that is not solely circumscribed in neocortical areas.

We have recently completed a study examining the N200 component of the ERP in abstinent alcoholics (Porjesz & Begleiter, 1981a, 1981b; Porjesz, Begleiter, Bihari, & Kissin, 1987). The N200 component is a modality-specific negative deflection with a maximum amplitude at occipito-parietal scalp for the visual modality, and at central regions for the auditory modality. Recent evidence suggests that the latency of N200 can be taken as an early index of stimulus evaluation time (Renault & Lesevre, 1979); the more difficult the discrimination, the longer the latency of N200 (Gaillard & Lawson, 1980; Ritter, Simson, Vaughan, & Friedman, 1979; Towey, Rist, Hakerem, Ruchkin, & Sutton, 1980). The N200 component is a better index of stimulus evaluation time than is reaction time (RT), because it is not confounded by the motor response. RT is a complex measure of speed of information processing, as it depends on the end product of stimulus evaluation, response selection and organization, and the motor response. Therefore, although there are some reports of delayed RTs in chronic alcoholics (Bertera & Parsons, 1973; Talland, 1963; Vivian, Goldstein, & Shelly, 1973), these studies cannot determine which aspect or aspects of information processing are slower in alcoholics.

We were interested in specifically examining the speed of stimulus evaluation in chronic alcoholics, using the N200 component of the ERP as an index. Therefore, we designed an RT study involving easy and difficult line-orientation discriminations. This visuospatial RT design enabled us to investigate the relationship among difficulty of discrimination, N200 latency, P300 characteristics, and RT in abstinent chronic alcoholics. ERPs were obtained to frequent nontargets (vertical line), and infrequent easy (90° deviant from vertical) and difficult (3° deviant) line orientations.

Our results indicated that the latency of N200 reflected difficulty of discrimination in the control subjects, being significantly delayed for the difficult as compared to the easy discrimination. However, it failed to do so

in the alcoholics, where N200 latencies were similar regardless of difficulty of discrimination. Furthermore, the N200 latency occurred significantly later in the alcoholic group than in the control group for both easy and difficult discriminations, suggesting that the alcoholics found the discrimination task more difficult, and hence needed more time for stimulus evaluation. The latency difference between groups was even more apparent for the easy discrimination than for the difficult discrimination. This suggests that the alcoholics needed proportionately more time to make an easy discrimination (vertical from horizontal) when compared to the controls (who could process this information more quickly) than to make a difficult discrimination (which both groups presumably found difficult).

In addition, alcoholics manifested delayed P300 latencies to easy discriminations when compared to controls; these P300 latencies were comparable to those expected for a difficult task. These results suggest that the alcoholics, finding all tasks difficult, adopted an undifferentiated mode of responding regardless of task requirements. While the amplitude of N200 was larger for easy discriminations than difficult discriminations in the control group, the amplitude of N200 was the same in the alcoholics regardless of task difficulty. The amplitude of N200 has been shown to be related to degree of stimulus deviance in normal subjects (Näätänen, Hukkanen, & Järvilehto, 1980).

There were no significant differences in RTs between the two groups of subjects, although the alcoholics tended to have somewhat faster RTs than controls. However, the alcoholics tended to make more errors, both in terms of false alarms and in terms of missing target stimuli, although these results were not significant. This response pattern indicates that speed was stressed over accuracy (Kutas, McCarthy, & Donchin, 1977), implying that the alcoholics adopted different response strategies from the controls. These results suggest a lack of inhibition in the chronic alcoholics, reflected by their apparent inability to withhold responding until certainty of accuracy or correctness was established.

In addition to these latency results, we found that alcoholics had significantly depressed P300 amplitudes. This low-amplitude P300 was even more apparent for the easy discrimination, where controls exhibited very high P300 voltages. The P300 voltage was significantly larger for the 90° target as compared to the 3° target in the control but not the alcoholic subjects. This result is predicted by many ERP studies, which have demonstrated that the more deviant a rare stimulus is from the background (the more easily discriminable it is), the larger the P300 amplitude (Ford *et al.*, 1979; Johnson & Donchin, 1978; Ritter, Simson, & Vaughan, 1972; Ruchkin & Sutton, 1978; Towey *et al.*, 1980). Perhaps the lack of P300 amplitude difference in the alcoholic group indicates that they were more uncertain of the correctness of their decision than were the controls, as they stressed

speed over accuracy. Furthermore, while controls manifested significant target–nontarget P300 measures, alcoholics did not.

Thus on the basis of both the N200 and P300 ERP components, it was concluded that alcoholics have difficulty evaluating the potential significance of a stimulus. The alcoholic subjects did not electrophysiologically differentiate between relevant and irrelevant, or easy and difficult discriminations but rather maintained the same ERP characteristics (both amplitude and latency), regardless of the task requirements. This perhaps indicates that alcoholics' template for match–mismatch decisions is lost or not readily available. In either case, it suggests a memory deficit in which each incoming stimulus must be evaluated anew. Our data suggests that alcoholics manifest both types of brain dysfunction: The delay in N200 latency suggests that the template for comparison is not as readily accessible in alcoholics, while the low P300 voltages suggest that once retrieved, the match–mismatch processes themselves are impaired in alcoholics.

Recovery of Evoked Brain Potentials with Abstinence

We are currently examining the reversibility of the BSP and ERP deficits observed at 1 month of abstinence and following 4 months of continued abstinence in the same hospitalized alcoholics (Porjesz, 1983; Porjesz & Begleiter, 1987). Preliminary data following 4 months of abstinence indicate improved morphology of BSP waveforms, shortening of latencies, and improved conduction times. However, group data indicate that these peaks are still occurring somewhat later than those of control subjects.

The relative roles of abstinence from alcohol and nutritional factors in so-called "recovery" still remain to be determined. Throughout the long-term abstinence program in our hospital, patients receive extensive vitamin therapy and may be manifesting improvements in nutritional status. Furthermore, the role of withdrawal cannot be overlooked; CNS hyperexcitability may be followed by a period of subacute hypoexcitability. We might speculate that this hypoexcitability may be manifested by a prolongation of brain stem latencies caused by aberrant fluidizing effects on the membranes, which may result in edema. It should be noted that edema resulting from osmotic stress can lead to demyelination (Feigen & Budzilovich, 1978, 1980; Kleinschmidt-DeMasters & Norenberg, 1981; V. Lewis, 1976; Yates, 1976).

However, it should be noted that those alcoholics who remain in treatment for the full 4 months have less impaired BSPs at initial testing (3–4 weeks) when the data are analyzed retrospectively. As we are only able to examine reversibility in alcoholics who remain in long-term treatment, and these alcoholics tend to be less impaired initially, we cannot be certain that recovery occurs in all alcoholics regardless of degree of impairment. It

remains to be determined whether recovery occurs as a function of the initial degree of impairment, whether greater impairment requires longer time periods for reversibility, or whether recovery ceases beyond a certain critical level of impairment.

While the BSP delays seem to improve with prolonged abstinence, the decreased voltages in the P300 component of the ERP do not seem to change with prolonged abstinence (Porjesz, 1983; Porjesz & Begleiter, 1987). We examined the possibility of reversibility of late-component P300 deficits in abstinent alcoholics following 3 weeks and 4 months of abstinence. Interestingly, no improvement in ERP morphology or late-component amplitude was noted following 4 months of abstinence in the same alcoholics; in fact, the waveforms were strikingly similar at initial test and retest. Furthermore, there was no improvement in the differential enhancement of P300 amplitudes on the basis of task relevance to target stimuli in these abstinent alcoholics. Thus, even following 4 months of abstinence, these alcoholics manifested abnormally low P300 amplitudes. We have observed these P300 decrements in response to both auditory and visual target stimuli following 3 weeks and 4 months of abstinence in a bimodal target-selection study. These results suggest that the P300 deficits may not be reversible, or may perhaps reverse much more slowly following very long abstinence periods. It is even possible that these P300 deficits may precede alcoholism, and may represent a predisposing factor differentiating those individuals with a susceptibility to alcoholism.

We are currently investigating electrophysiological aberrations in another group of nonhospitalized alcoholics sober for 3–10 years, and have found that they manifest normal BSPs. This suggests that perhaps 4 months is not a long enough time interval to investigate reversibility of brain dysfunction following years of heavy drinking. However, it should be noted that these long-term abstinent alcoholics were not tested initially, and therefore the extent of BSP aberration they may have manifested immediately following alcohol abuse is not known. It is possible that these alcoholics never exhibited BSP delays, as we do not see BSP delays in all alcoholics tested. While the issue of reversibility is still unresolved, the data seem to indicate slow reversibility of BSP deficits with prolonged abstinence. However, as P300 deficits were still observed following the same prolonged sobriety period (more than 3 years), the data suggest no recovery of P300 deficits following long-term abstinence. This it seems that some electrophysiological aberrations observed in chronic alcoholics improve with prolonged abstinence, while other electrophysiological aberrations do not change with prolonged sobriety. Caution is suggested in interpreting the results, as they are based on small samples. We are currently continuing to examine this issue with larger sample sizes in an effort to determine the important factors of susceptibility and reversibility of brain dysfunction in alcoholism.

Possible Evoked Brain Potential Markers for Alcoholism

It has generally been assumed that the brain abnormalities observed in alcoholics are due to the toxic effects of alcohol on the brain, nutritional deficits, or an interaction of alcohol and nutrition-related factors. The possibility that these brain deficits may in fact precede alcohol abuse has only been suggested recently. There is increasing evidence that certain individuals are at high risk for developing alcoholism. Specifically, sons of alcoholic fathers are four times more likely to develop alcoholism than sons of nonalcoholics (Goodwin, 1979; Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973), even when they are separated from their biological parents soon after birth. Studies of male adoptees indicate that the biological rather than the adoptive parent is predictive of later drinking problems (Bohman, 1978; Cadoret & Gath, 1978; Cadoret, Cain, & Grove, 1980; Goodwin & Guze, 1974; Goodwin *et al.*, 1973; Schuckit, Goodwin, & Winokur, 1972). Furthermore, the concordance rate for alcohol abuse among identical twins is almost double the rate for fraternal twins (Kaij, 1960); patterns of alcohol consumption have also been found to be highly concordant among identical twins (Jonsson & Nilsson, 1968; Loehlin, 1972; Partanen, Brun, & Markkamen, 1966). Taken together, these studies suggest that a genetic factor predisposing sons of alcoholics to alcoholism may be involved.

The identification of a suitable biological marker or markers that is genetically transmitted would provide more definitive evidence that the etiology of alcoholism involves genetic factors. It is very likely that brain function is involved in the genetic predisposition for alcoholism. There is good evidence to indicate that brain EP waveforms are genetically determined. Monozygotic twins manifest EP waveforms that are as concordant with each other as EPs obtained from the same individual tested twice (Dustman & Beck, 1965).

We have recently undertaken a major project to investigate the possibility that sons of male alcoholics manifest differences in EPs that antedate any exposure to alcohol. In order to study this problem, we are recording EPs and ERPs in boys between the ages of 6 and 18 and comparing electrophysiological responses from sons of alcoholics (high-risk) and age- and education-matched sons of nonalcoholics (low-risk). Children whose mothers abused alcohol are excluded in order to rule out the contribution of the fetal alcohol syndrome.

In one ERP study (Begleiter, Porjesz, Bihari, & Kissin, 1984) we examined the P300 component in boys between the ages of 7 and 13 who had no prior experience with alcohol. The high-risk group consisted of 25 sons of alcoholic fathers with a mean age of 11.9 ($SD = 2.1$). In each case, the father had received the exclusive diagnosis of alcoholism (DSM-III) and had been in treatment for alcoholism at some time. Boys whose mothers had

ingested alcohol during pregnancy or who drank excessively after giving birth were excluded. Only boys without medical problems and without exposure to alcohol or other substances of abuse were included in this study. The 25 normal control subjects were boys who were matched for socioeconomic status and age to the high-risk subjects. The control group had a mean age of 12.5 years ($SD = 2.4$). They were included only if they had no exposure to alcohol or other substances of abuse, and had no history of alcoholism or other psychiatric disorder in first- or second-degree relatives. Except for alcohol history, the same exclusion criteria were used as for the high-risk group.

The experimental design consisted of a visual head-orientation task. The nontarget stimulus was a frequently occurring oval presented in the center of a computer-generated display. The target stimulus was a rarely occurring aerial view of the head with the nose and one ear drawn in, rotated in four possible positions: nose up and right ear, nose up and left ear, nose down and right ear, nose down and left ear. Subjects pressed one of two microswitches as quickly and accurately as possible (RT) with either the right or left index finger to indicate whether the right or left ear was present on the display, respectively. In the "easy" condition, the head was facing forward (nose up on the screen) and the left or right ear appeared on the same side that corresponded to the appropriate button; in the "difficult" condition, the head was facing back (nose down on the screen) and the left or right ear appeared on the side opposite the corresponding button.

RTs for easy stimuli were significantly shorter than for difficult stimuli ($p < .0001$); there were no significant RT differences between groups. However, the number of correct behavioral responses was significantly less for the high-risk group for easy ($p < .001$) and difficult stimuli ($p < .001$). The entire raw data set was subjected to a principal-components analysis with varimax rotation using the covariance matrix. Basis waveforms were extracted, and the component scores for each of the four factors were then subjected to an analysis of variance. Our results indicated that only the factor representing the P300 component was significantly different between the high- and low-risk groups; the P300 amplitudes were found to be significantly smaller in the high-risk group as compared to the control group. This group difference was found to be significant at the parietal electrode (where P300 is maximum) for both the easy condition ($p < .01$) and the difficult condition ($p < .002$). These findings are the first to indicate a significant difference in P300 amplitude between boys at high risk for alcoholism and normal control boys, without exposure to alcohol.

Differences in electrophysiological recordings in response to challenge doses of alcohol have recently been reported between males with some family history of alcoholism and control subjects. This has been reported for EEG (Pollock *et al.*, 1983) and ERP (Elmasian, Neville, Woods, Schuckit, & Bloom, 1982) recordings. In a study conducted at the Salk Institute, Elmasian *et al.* (1982) found that male college students with family

histories of alcoholism manifested different ERPs to challenge doses of both placebo and alcohol, when compared to matched controls without a family history of alcoholism; these differences between the two groups were apparent in the P300 component.

Our findings are particularly interesting, as they were obtained without the use of alcohol. We found that approximately 36% of the sons of alcoholics manifested this P300 difference. However, whether these low-amplitude ERPs are in fact markers for a predisposition to alcoholism remains to be tested. Studies are under way in our laboratory to retest these children each year to determine whether those manifesting ERP differences are in fact those who go on to develop problems with alcohol.

It is interesting to note that the P300 deficits we have observed in abstinent alcoholic patients are also present in some boys at high risk for alcoholism. We were interested in determining whether other electrophysiological deficits observed in alcoholic patients would be apparent in boys at risk for alcoholism. As we have observed brain stem abnormalities in abstinent alcoholics (Begleiter *et al.*, 1981), we decided to record BSPs in high-risk boys.

In this study (Begleiter, Porjesz, & Bihari, in press) we examined another sample of 23 sons of alcoholic fathers between the ages of 7 and 13 with a mean age of 12.2 ($SD = 2.1$). The 23 normal control subjects were boys who were matched for socioeconomic status, age, and education to the high-risk boys. The control group had a mean age of 12.4 ($SD = 2.3$). The inclusion and exclusion criteria were identical to those previously described for the P300 study. Again, we only included boys without prior exposure to alcohol or other illicit drugs. As in our study with alcoholics, the latency of the first five positive peaks and the interpeak latencies between peak 1 and each successive peak were measured.

We did not find any differences in the auditory BSPs obtained from sons of alcoholic fathers and those obtained from matched control subjects. The individual peak latencies and the brain stem transmission times were found to be similar in the two groups. The lack of significant differences in BSPs between high-risk and control subjects is interesting in light of our observed difference in P300 between high-risk and control subjects. These findings indicate that while P300 deficits may be antecedents of the development of alcoholism in some high-risk individuals, the brain stem deficits that we have observed in abstinent alcoholics are most probably alcohol-related changes. Further evidence for this hypothesis is provided by our findings that the BSP abnormalities observed in abstinent alcoholics seem to "recover" with prolonged abstinence, while the P300 deficits do not.

Conclusion

It remains for future research to separate those brain aberrations that are antecedents of alcohol abuse from those that are the consequences of years

of heavy drinking. It is not known at the present time which innate differences determine responsiveness to alcohol, including predisposition to alcohol abuse. Genetic differences in strains of animals have been found to determine whether they are predisposed to drink alcohol or find it to be aversive (Rogers, 1972). Furthermore, differences in neurophysiological responses to alcohol have been reported in different genetic rat strains (Sorenson, Palmer, Dunwiddie, & Hoffer, 1980). Humans have also been found to differ in their responsiveness to alcohol—for example, in augmenting–reducing (Buchsbaum & Ludwig, 1980; Spilker & Callaway, 1969), in family history of alcoholism (Elmasian *et al.*, 1982; Pollock *et al.*, 1983), and in flushing–nonflushing (Fukui *et al.*, 1981). For example, recent findings in Japan indicate that "flushers" (those who manifest an adverse flushing reaction to alcohol) are more susceptible to delayed BSPs than "nonflushers" when ingesting a challenge dose of alcohol (Fukui *et al.*, 1981). It is possible that the low P300 amplitudes we have observed in young sons of alcoholics represent a vulnerability marker that may only become apparent in response to alcohol. For example, it is possible that although we did not observe BSP differences between boys at high and low risk for alcoholism without the ingestion of alcohol, BSP differences may become apparent once alcohol is introduced. It may in fact be those boys who manifest P300 decrements without alcohol who will respond differently to alcohol on other EP measures (e.g., BSPs). Studies are under way in our laboratory to test adolescents with family histories of alcoholism under the influence of challenge doses of alcohol with a full battery of EP tests.

The ability to utilize sophisticated neurophysiological tools to assess brain dysfunction in abstinent alcoholics and individuals at risk for alcoholism may prove most valuable in separating the deleterious effects of alcoholism on the CNS from the brain deficits that may be antecedents of the development of alcoholism. The delineation of similar neurophysiological deficits in abstinent alcoholics and children at high risk for alcoholism may be of fundamental importance in the identification of possible genetic marker(s). The search for a possible cluster of neurophysiological deficits in children at high risk for alcoholism is presently under way in our laboratory.

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