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The Use of Event-Related Potentials In the Study of Alcoholism: Implications for the Study of Drugs of Abuse

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While it has long been apparent that the human brain is susceptible to both the acute and chronic effects of alcohol, it is only recently, with the development of sophisticated computer-assisted technology, that these effects can be studied in vivo. With the use of this technology, evoked brain potentials (EPs) can be studied to examine more subtle forms of brain damage and/or dysfunction by examining the relation of an EP to a specific sensory or behavioral event. Event-related potentials (ERPs) 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 with a non-invasive scalp electrode the time-locked brain electrical activity that follows 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 (i.e., the ERPs) from the background random "noise," which is canceled out with these procedures. Depending on stimulation parameters 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 and integrity.

ERP techniques have proven to be especially valuable in indexing electrophysiological concomitants of complex cognitive tasks (Hillyard et al. 1978; Donchin 1979; Donchin et al. 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 computerized axial tomography (CT-scan) or nuclear magnetic resonance (NMR) 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 scans. As a result, ERP aberrations are often observed in the absence of brain damage as visualized on CT-scan.

In order to consider how EP techniques may be used to study problems of drug abuse, it may be useful to examine how they have been used to study the effects of alcohol on the brain. EP techniques have provided indices sensitive to the various alcohol effects, namely: alcoholization, tolerance, withdrawal, and long-term brain dysfunction resulting from chronic alcohol use. Alcoholization is characterized by marked decreases in EP amplitude (Bierley et al. 1980) and prolongations in conduction velocities of the brain stem potential (BSP) (Squires et al. 1978a, 1978b; Chu et al. 1978). Chronic alcohol intake is also accompanied by EP amplitude reductions (Porjesz et al. 1976; Begleiter and Porjesz 1977) and by BSP delays that are less pronounced once tolerance develops (Squires et al. 1978a, 1978b; Chu et al. 1978; Zilm et al. 1981). Withdrawal is characterized by increased EP voltages and extremely shortened BSP latencies, suggestive of underlying CNS hyperexcitability (Begleiter and Porjesz 1977, 1979; Begleiter et al. 1980a; Squires et al. 1978a, 1978b; Chu et al. 1978; Hunter and Walker 1980). Finally, long-term abstinence is marked by decreased EP amplitudes (hyporeactivity) and prolonged BSP latencies and slower conduction velocities (Begleiter et al. 1981; Porjesz and Begleiter 1983). The duration of these prolonged central nervous system (CNS) disturbances and their potential recovery are not yet known.

We have recently recorded auditory BSP's from hospitalized alcoholics who were abstinent from alcohol for 1 month (Begleiter et al. 1981). This technique allows investigation of subcortical brain functioning with a noninvasive scalp electrode (Sohmer and Feinmesser 1967; Jewett 1970; Jewett and Williston 1971). These "far-field" potentials consist of 7 time-locked positive waves, (designated I to VII), each presumed to reflect activity at different sites along the auditory pathway from the auditory nerve through the brain stem (Jewett 1970; Lev and Sohmer 1972; Buchwald and Huang 1975; Starr and Achor 1975; Starr and Hamilton 1976; Stockard and 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 first peak and peak V of the inferior colliculus is most often taken as a measure of brain stem transmission time (Fabiani et al. 1979).

In our study, we found that alcoholic patients manifested significant delays in latencies and central conduction velocities of peaks II to V. These findings are remarkably similar to those reported with acute doses of alcohol in animals (Squires et al. 1978a) and man (Squires et al. 1978b). Our study provided 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 et al. 1959) and has been observed in rats chronically exposed to alcohol (Moscatelli and Demediuk 1980). Similar results have recently been reported in neurologically impaired alcoholics (Rosenhamer and Silfverskiold 1980; Chu and Squires 1980; Nickel and Ludewig 1981; Haas and Nickel 1981; Chu et al. 1982), and in neurologically intact alcoholics (Cassvan et al. 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, and nutritional factors) 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 because nutritional deficits are known to lead to demyelinating diseases such as polyneuropathy (Hillman 1974). At present, we are investigating the relationship between drinking history, nutritional factors, and the magnitude of BSP aberration. Our preliminary data suggest that alcoholics with signs of nutritional deficits and/or polyneuropathy display different BSP waveforms than those alcoholics without nutritional deficits. Furthermore, length of drinking history does not seem to correlate with BSP delay; in fact, alcoholics with relatively short heavy drinking histories ($<$ 8 years) and evidence of nutritional deficits manifested greater BSP aberrations than alcoholics with long drinking histories ($>$ 20 years) and no signs of nutritional deficits. The results of animal studies (Chu et al. 1978) suggest that other factors besides chronic alcohol exposure are necessary to produce BSP abnormalities; chronic alcohol ingestion was not sufficient to cause BSP delays after withdrawal in laboratory animals that did not also have nutritional deficits. Taken together, these findings suggest that BSP aberrations in alcoholics may be the result of alcohol and/or nutritional factors.

For the past several years, we have also systematically examined ERPs in medication-free alcoholics who are 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 which has been well documented to vary predictably under specific conditions in normal subjects (Hillyard et al. 1978; Donchin 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 N1 component of the ERP (Porjesz and Begleiter 1979), which occurs at around 100 msec. The N1 component is sensitive to attention to a relevant stimulus modality; it is enhanced to

all stimuli in a relevant stimulus modality, and reduced to stimuli in irrelevant modalities (Hillyard et al. 1973, 1978; Picton and Hillyard 1974). The patient was presented with a sequence of randomized single flashes and clicks with rarely occurring double flashes and clicks interspersed among them. The patient was required to "shift attentional sets," in order to count either the double flashes or double clicks, or ignore all stimuli, in an otherwise identical stimulus sequence.

Consistent with the ERP literature (Hillyard et al. 1973, 1978), control subjects in our study manifested significantly enhanced N1 components to stimuli in the relevant as compared to the irrelevant modality; however, alcoholics maintained the same low amplitude of N1 regardless of the degree of task relevance. Often it is the differential voltage between ERPs recorded 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. These results suggest that alcoholics may be incapable of appropriate "sensory filtering," as they do not differentiate neurophysiologically between relevant and irrelevant channels.

In addition, the results indicated that abstinent alcoholics manifested abnormally reduced late component amplitudes ($\geq$ 100 msec), but not early component amplitudes. These findings in abstinent alcoholics are remarkably similar to results obtained when healthy subjects ingest single doses of alcohol (Lewis et al. 1969; Porjesz and Begleiter 1975; Rhodes et al. 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.

We have also used the P3 component of the ERP in many different experimental paradigms to examine brain dysfunction in alcoholics (figure 1). The P3 or P300 component is a large, positive deflection that occurs approximately 300 msec to 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 et al. 1967), unpredictability (Donchin et al. 1978) and infrequency (Tueting et al. 1971), as well as by motivational factors (Begleiter et al. 1983). The characteristics of P3 are unrelated to stimulus parameters, and can even be elicited in the absence of an expected stimulus (emitted potentials) (Klinke et al. 1968). In terms of scalp topography, P3 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 et al. 1976, 1977a, 1977b).

In one of our laboratory studies, we investigated the P3 component with a visual target-selection paradigm (Porjesz et al. 1980). The target-selection paradigm is most frequently used to

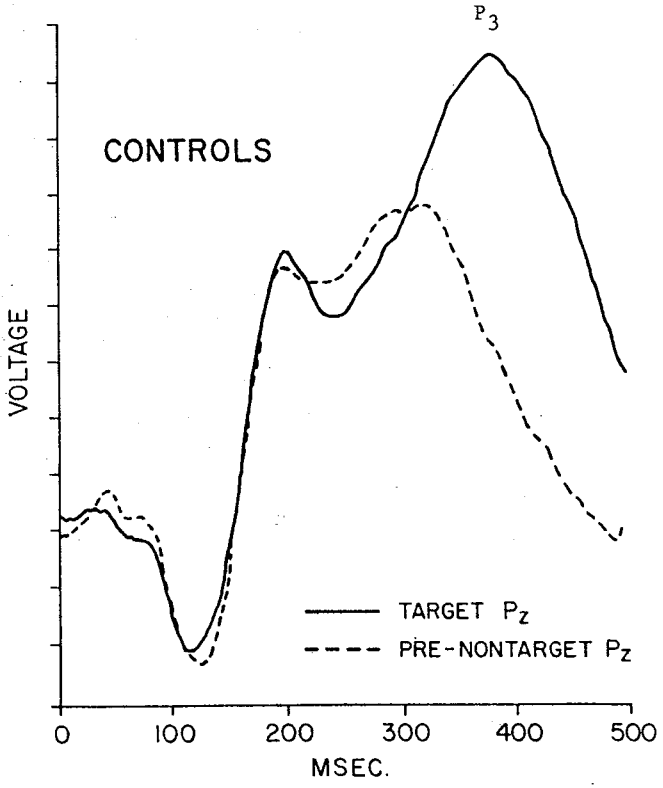

FIGURE 1

Grand mean ERP wave forms recorded at parietal electrode (Pz) to the target stimulus (solid line) and nontarget stimulus (dashed line) in healthy subjects. Notice the prominent P3 component (large positive deflection occurring between 300 and 450 msec) to the target stimulus.

elicit a P3 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 N1 components, but no P3, while rare target stimuli elicit both N1 and P3 components (figure 1). In our study (Porjesz et al. 1980), the stimuli were geometric shapes. One rare geometric shape (e.g., triangle) was designated target, and the subject was required to press a button only in response 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 targets (rarely occurring, task-relevant geometric shapes), nontargets (frequently occurring task irrelevant geometric shapes), and novel stimuli (rarely occurring task irrelevant random shapes).

We found that P3 amplitudes were significantly reduced or absent in alcoholic patients to rare target stimuli under conditions optimal for eliciting large P3s (Donchin et al. 1978) (figure 2). This finding was most pronounced over parietal areas, where P3 amplitude is maximal at scalp (Simson et al. 1977a, 1977b; Ritter et al. 1968). Furthermore, while controls manifested differentially enhanced P3 components to target stimuli, alcoholics manifested identical low amplitude P3 waves with the same P3 latencies, regardless of whether a stimulus was a target or nontarget. Moreover, despite the fact that all stimuli were in the relevant channel, we found that the N1 amplitudes were significantly reduced in alcoholics to all stimuli, to levels comparable to an irrelevant stimulus modality. As in our bimodal study (Porjesz and Begleiter 1979), this suggests that sensory-filtering mechanisms are impaired in chronic alcoholics.

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.

Recent evidence implicates the amygdala and hippocampus as possible neural generators of P3. One recent study investigating the neural origins of P3 with implanted electrodes in humans reported that P3 was maximum at subcortical loci (Wood et al. 1980). Similarly, Halgren et al. (1980) have recently recorded large late potentials from limbic system with implanted electrodes in humans. They postulate that P3 may be generated in hippocampus or amygdala. Magnetoencephalographic studies have also suggested the hippocampus as a possible neural generator of the P3 component (Okada et al. 1983).

Thus, our results that alcoholics manifest low-voltage or even absent P3 components under conditions designed to elicit maximum P3 component amplitudes may be indicative of hippocampal

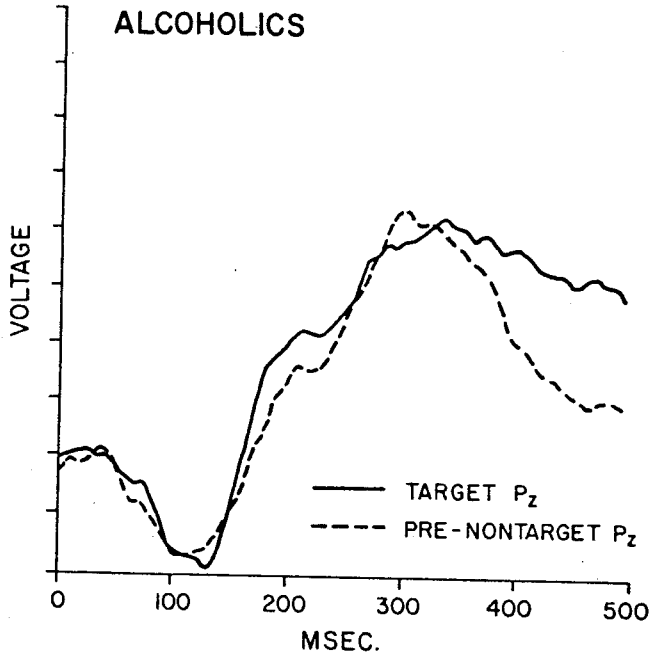

FIGURE 2

Grand mean ERP wave forms recorded at parietal (Pz) to the target (solid line) and nontarget (dashed line) stimuli in the alcoholic group. Compare the P3 component of the target stimulus to that of the control group (figure 1), and notice how reduced it is in amplitude. Also notice the lack of difference between P3 amplitudes to target and nontarget stimuli in the alcoholic group in this figure.

deficits. While these results do not rule out the contributions of neocortical sites, they emphasize the important role of limbic structures in generating the P3 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 et al. 1980a; Walker et al. 1980, 1981; Riley and Walker et al. 1978). Long-term ethanol consumption has been found to result in the loss of dendritic spines in the hippocampus of both the mouse (Riley and Walker 1978) and rat (Walker et al. 1980). In our laboratory, we have also demonstrated a hippocampal susceptibility to both acute and chronic alcohol effects with EPs recorded from monkey hippocampus (Begleiter et al. 1980a).

We were interested in determining the relationship between electrophysiological deficits and structural deficits assessed with CT-scan in alcoholics (Begleiter et al. 1980b). 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 P3 paradigm previously described (Porjesz et al. 1980). Alcoholics with enlarged cortical sulci (Pos-CT) had significantly reduced (or absent) P3 amplitudes to target stimuli, as compared to alcoholics without signs of enlarged cortical sulci (Neg-CT); however, both groups manifested smaller P3s to targets than did control subjects. Furthermore, both groups of alcoholics displayed similar P3 components to all categories of stimuli, regardless of task relevance.

Because Neg-CT alcoholics also manifested diminished P3 amplitudes when compared to healthy nonalcoholics, neocortical shrinkage alone cannot explain these P3 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 also manifest hippocampal deficits. This, perhaps, lends support to the hypothesis that alcohol produces diffuse brain damage not solely circumscribed to neocortical areas.

We have recently completed a study examining the N2 or N200 component of the ERP in abstinent alcoholics (Porjesz and Begleiter 1981a, 1981b; Porjesz and Begleiter, in press). The N2 component is a modality-specific negative deflection with a maximum amplitude at occipitoparietal scalp for the visual modality and at central regions for the auditory modality.

Recent evidence suggests that the latency of N2 can be taken as an early index of stimulus evaluation time (Renault and Lesevre 1979); the more difficult the discrimination, the longer the latency of N2 (Ritter et al. 1979; Towey et al. 1980; Gaillard and Lawson 1980). This component is thus a better index of stimulus evaluation time than the reaction time (RT), because it is not confounded by the motor response. The 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 motor response. Therefore, although there are some reports of delayed RTs in chronic alcoholics (Talland 1963; Vivian et al. 1973; Bertera and Parsons 1973), these studies cannot determine which aspect(s) of information processing is (are) slower in alcoholics.

In order to use the N2 component of the ERP as an index of speed of stimulus evaluation, we designed an RT study involving easy and difficult line orientation discriminations. This visuospatial RT design enabled us to investigate the relationship between difficulty of discrimination, N2 latency, P3 characteristics, and RT in abstinent alcoholics. ERPs were obtained to frequent nontarget (vertical line), and infrequent easy (90 degree deviant from vertical) and difficult (3 degree deviant) line orientations.

Our results indicated that the latency of N2 reflected difficulty of discrimination in the control subjects, being significantly delayed to the difficult when compared to the easy discrimination. By contrast, it failed to do so in the alcoholics, where N2 latencies were similar regardless of difficulty of discrimination. Furthermore, the N2 latency occurred significantly later in the alcoholic group than in the control group for both easy and difficult discriminations, suggesting that alcoholics need more time for stimulus evaluation and may therefore find the discrimination task more difficult. The latency difference between groups was even more apparent for the easy discrimination than for the difficult discrimination. This suggests that alcoholics need proportionately more time to make an easy discrimination (vertical from horizontal) when compared to controls (who can process this information more quickly), than to make a difficult discrimination (which both groups presumably find difficult).

In addition, alcoholics manifested delayed P3 latencies to easy discriminations when compared to controls; these P3 latencies were comparable to those expected for a difficult task. These results suggest that alcoholics adopt an undifferentiated mode of responding regardless of task requirements, finding all tasks difficult. While the amplitude of N2 was larger for easy discriminations than difficult discriminations in the control group, the amplitude of N2 was the same in the alcoholics regardless of task difficulty. The amplitude of N2 has been

shown to be related to the degree of stimulus deviance in normal subjects (Naatanen 1981).

There were no significant differences in RTs between the two groups of subjects, although the alcoholics tended to have faster RTs and make more errors than controls. This response pattern implies that alcoholics adopt different response strategies from controls, stressing speed over accuracy (Kutas et al. 1977). Their apparent inability to withhold responding until certainty of accuracy or correctness has been established suggests a lack of inhibition in alcoholics.

In addition to these latency results, we found that alcoholics had significantly decreased P3 amplitudes. This low amplitude P3 was even more apparent for the easy discrimination, where controls exhibited very high P3 voltages. The P3 voltage was significantly larger for the 90 degree target when compared to the 3 degree 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 P3 amplitude (Towey et al. 1980; Ritter et al. 1972; Ford et al. 1979; Johnson and Donchin 1978; Ruchkin and Sutton 1978). Perhaps the lack of P3 amplitude difference in the alcoholic group indicates that they are more uncertain of the correctness of their decision than are controls, as they stress speed over accuracy.

Thus, on the basis of both the N2 and P3 ERP components, it was concluded that alcoholics have difficulty evaluating the potential significance of a stimulus. They do not electrophysiologically differentiate between relevant and irrelevant or easy and difficult discriminations, but rather maintain the same ERP characteristics (both amplitude and latency) regardless of the task requirements. This perhaps indicates that their template for match/mismatch decisions is lost or not readily available. In either case, it suggests a memory deficit where each incoming stimulus must be evaluated anew. Our data suggest that alcoholics manifest both types of brain deficits: the delay in N2 latency suggests that the template for comparison is not as readily accessible in alcoholics, while the low P3 voltages suggest that once retrieved, the match/mismatch processes themselves are impaired in alcoholics.

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 and Begleiter, in preparation). Preliminary data following 4 months of abstinence indicate improved morphology of BSP waveforms, shortening of latencies, and improved conduction times.

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 is manifested by a prolongation of brain stem latencies caused by aberrant fluidizing effects on the neuronal membranes which may result in edema. Edema resulting from osmotic stress can lead to demyelination (Lewis 1976; Yates 1976; Feigen and Budzilovich 1978, 1980; Kleinschmidt-DeMasters and Norenberg 1981).

However, it should be noted that those alcoholics who remained in treatment for the full 4 months had less impaired BSPs at initial testing (3 to 4 weeks) when the data were analyzed retrospectively. As we are only able to examine reversibility in alcoholics who remained 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.

We are currently investigating electrophysiological aberrations in another group of nonhospitalized alcoholics sober from 3 to 10 years, and thus far we 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 ($>$ 3 years) were not tested initially; 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.

Although the BSP delays seem to improve with prolonged abstinence, the decreased voltages in the P3 component of the ERP do not seem to change with prolonged abstinence (Porjesz 1983; Porjesz and Begleiter, in preparation). We examined the possibility of reversibility of late component P3 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 P3

amplitudes on the basis of task relevance to target stimuli in these abstinent alcoholics. In addition, P3 deficits were still observed in our group of nonhospitalized alcoholics sober from 3 to 10 years. Thus, even following 3 to 10 years of abstinence, alcoholics still manifest abnormally low P3 amplitudes. We have observed these P3 decrements in response to both auditory and visual target stimuli in a bimodal target-selection study. These results suggest that the P3 deficits may not be reversible, or perhaps reverse much more slowly following very long abstinence periods.

Thus, it seems that some electrophysiological aberrations observed in 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 examining this issue with larger sample sizes in an effort to determine the important factors of susceptibility and reversibility of brain dysfunction in alcoholism.

As these P3 deficits do not seem to recover following prolonged sobriety ($>$ 3 years), it is even possible that these deficits may precede the development of alcoholism. While 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 nutritional-related factors, these brain deficits may represent a predisposing factor differentiating those individuals with a susceptibility to alcoholism. 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 et al. 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 (Goodwin et al. 1973; Bohman 1978; Cadoret and Gath 1978; Cadoret et al. 1980; Goodwin and Guze 1974; Schuckit et al. 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 (Partanen et al. 1966; Jonsson and Nilsson 1968; Loehlin 1972). Taken together, these studies suggest that a genetic factor predisposing sons of alcoholics to alcoholism may be involved.

An exciting use of EP techniques is in identifying possible biological marker(s) for those at risk for developing alcoholism. It is 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, for example, manifest EP waveforms that are as concordant with each other as EPs obtained from the same

individual tested twice (Dustman and Beck 1965).

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

In one ERP study (Begleiter et al. 1984), we examined the P3 component in boys between the ages of 7 to 13 who had no prior experience with alcohol. The high-risk (HR) group consisted of 25 sons of alcoholic fathers with a mean age of 11.9 (S.D. = 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 (NC) were boys who were matched for socioeconomic status (SES) and age to the HR subjects. The NC group had a mean age of 12.5 years (S.D. = 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 HR group.

The experimental design consisted of a visual head orientation task (figure 3). Subjects pressed one of two microswitches as quickly and accurately as possible (reaction time) with either the right or left index finger to indicate whether the right or left ear was present on the display, respectively. They performed this task under randomized "easy" and "difficult" conditions.

Reaction times for easy stimuli were significantly shorter than for difficult stimuli ($p < .0001$); there were no significant reaction time differences between groups. However, the number of correct behavioral responses was significantly less for the HR group for easy ($p < .001$) and difficult stimuli ($p < .001$). The entire raw data set was subjected to a principal component analysis with varimax rotation using the covariance matrix (PCAV). Basis waveforms were extracted, and the component scores for each of the four factors were then subjected to an analysis of variance (ANOVA). Our results indicated that only the factor representing the P3 component was significantly different between the high- and low-risk groups; the P3 amplitudes were found to be significantly smaller in the HR group as compared to the NC group. This group difference was found to be significant at the

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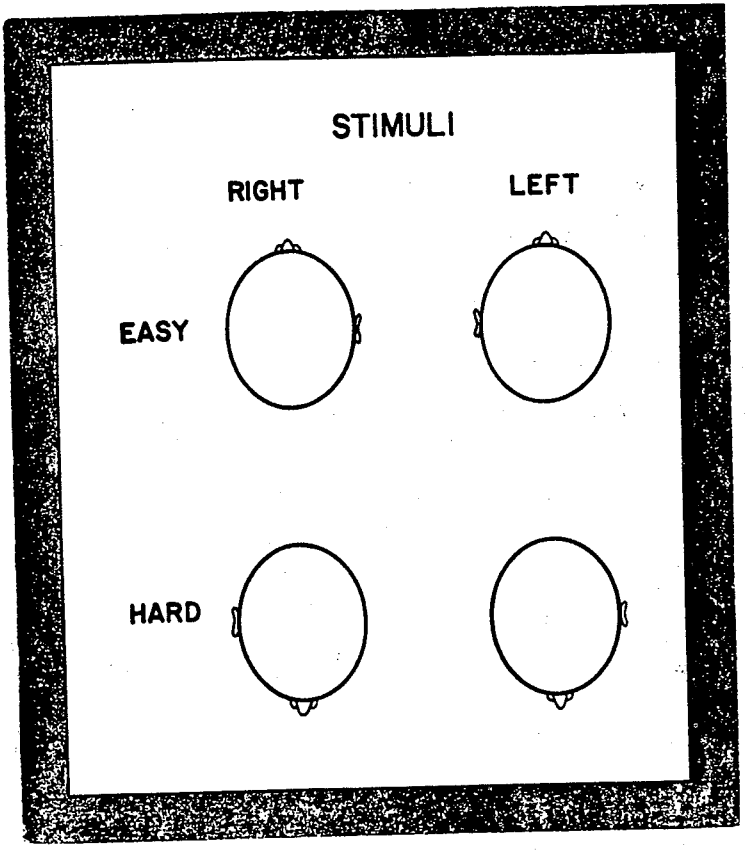

FIGURE 3

Experimental paradigm for head-orientation task. The target stimulus is 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 drawn in. The nontarget stimulus is a frequently occurring oval presented in the center of a computer-generated display. In the "easy" condition, the head was facing forward (nose up on the screen) and the left ear 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. The subject's task was to press the button corresponding to the ear present in the display as quickly as possible.

parietal electrode (where P3 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 P3 amplitude between boys, not exposed to alcohol, who are at high risk for alcoholism and normal controls.

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 et al. 1982) recordings. In the ERP study, Elmasian et al. 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 P3 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 P3 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 actually develop problems with alcohol.

Because of these findings, we were interested in determining whether other electrophysiological deficits observed in alcoholic patients would be apparent in boys at risk for alcoholism. Therefore, we decided to record BSPs in high-risk boys. In this study (Begleiter et al., in preparation), we examined another sample of 23 sons of alcoholic fathers between the ages of 7 and 13 with a mean age of 12.2 (S.D. = 2.1). The 23 NCs were boys who were matched for SES, age and education to the HR boys. The NC group had a mean age of 12.4 (S.D. = 2.3). The inclusion and exclusion criteria were identical to those previously described for the P3 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 I 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 HR and NC subjects is interesting in light of our observed difference in P3 between HR and NC subjects. These findings indicate that, while P3 deficits may antecede the development of alcoholism in some high-risk individuals, the brain stem deficits which we have observed in abstinent alcoholics are most probably

alcohol-related changes. Further evidence for this hypothesis is obtained by our findings that the BSP abnormalities observed in abstinent alcoholics seem to "recover" with prolonged abstinence, while the P3 deficits do not.

It remains for future research to separate those brain aberrations that antecede alcohol abuse from those that are the consequence of years of heavy drinking. It is not now known 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 were predisposed to drink alcohol or to find it aversive (Rogers 1972). Furthermore, differences in neurophysiological responses to alcohol have been reported in different genetic rat strains (Sorenson et al. 1980). Humans have also been found to differ in their responsiveness to alcohol, e.g., augmenting/reducing (Spilker and Callaway 1969; Buchsbaum and Ludwig 1980), family history for alcoholism (Elmasian et al. 1982; Pollock et al. 1983), and flushers/non-flushers (Fukui et al. 1981). For example, recent findings in Japan indicate that flushers (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.). It is possible that the low P3 amplitudes we observe in young sons of alcoholics represent a vulnerability marker which 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 P3 decrements without alcohol that will respond differently to alcohol on other evoked potential measures (e.g., BSP). 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 evoked potential 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 which may antecede 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.

We have recently begun to examine recovering drug addicts with the use of the same EP techniques. We reasoned that if these techniques are so sensitive in delineating the effects of alcohol on the brain (intoxication, withdrawal, long-term deficits), they would be ideal to study whether or not other substances of abuse

produce long-lasting effects on the brain.

Thus far we have examined narcotic addicts with an auditory oddball paradigm designed to examine the P3 component of the ERP. The addicts were males (mean age 35.5) who were drug-free for a minimum of 1 week. We found that recovering narcotic addicts manifest lower P3 amplitudes than matched control subjects. To the best of our knowledge, this is the first demonstration of a neurophysiological anomaly in drug addicts. These preliminary data from our laboratory run counter to the popular notion that chronic intake of narcotics may not result in CNS deficits. This popular tenet is not based on the presence of scientific evidence but has emerged in large measure in the absence of rigorous clinical or scientific data.

The ability to assess the integrity of various CNS systems with event-related brain potentials can provide valuable clinical information about the effects of chronic drug intake on CNS activity. ERP studies of abstinent drug addicts (heroin, cocaine, PCP, amphetamine, etc.) should result in fundamental information on the neurophysiological effects of various drugs of abuse. The neurophysiological delineation of the effects of various drugs of abuse on the human brain may help elucidate the resulting pathophysiology as well as provide data on possible etiological factors.

If, as appears to be the case with alcoholism, there are antecedent brain anomalies related to drug abuse, the neurophysiological data obtained from drug abusers would be of fundamental utility in the search for possible vulnerability factors.

Our current electrophysiological data in abstinent alcoholics and subjects at risk for alcoholism, as well as our preliminary event-related potential data in drug abusers, certainly warrant further neurophysiological investigations of CNS function in drug abusers. These preliminary findings encourage us to examine recovering addicts dependent on different substances of abuse (e.g., heroin, cocaine), to investigate possible neurophysiological aberrations.

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