Evoked Brain Potentials in Abstinent Alcoholics and Boys at Risk for Alcoholism

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Over the past several years, it has become evident that the brain is susceptible to the effects of alcohol, both acute and chronic. A good many of these effects can be studied in animals; however, as alcoholism is a uniquely human condition, it is important to investigate clinical symptoms of alcohol–related brain dysfunction with neurobiological techniques in alcoholic patients.

It should be noted that the relative inaccessibility of the living human brain to direct neurobiological scrutiny makes it difficult to conduct extensive studies of alcohol–related brain dysfunction in man. The recent development of sophisticated computer technology has made it possible to investigate functional deficits of the brain with evoked brain potential techniques. Evoked brain potentials are obtained by recording the brain's electrical response to a particular stimulus or event with noninvasive scalp electrodes. These evoked potential (EP) techniques permit an examination of more subtle forms of brain dysfunction that had heretofore been unobtainable. The evoked potential and event-related potential (ERP) techniques offer a unique approach for assessing level of brain functioning, as they permit the simultaneous observations of electrophysiology and behavior. The quantitative measurement of salient features extracted from EP and ERP recordings reflects various aspects of brain function related to integrative processes as well as the functional integrity of different neuroanatomical systems.

ERP techniques have been useful in indexing electrophysiological concomitants of complex cognitive processes. Electroencephalographic activity has been proven to be sensitive to the various central nervous system (CNS) dynamics reflecting alcohol–related effects, namely, acute alcohol effects, tolerance, withdrawal, and long–term brain dysfunction (Begleiter and Porjesz 1979; Zilm et al. 1981). For a review of the various effects of alcohol on brain electrical activity, the reader is referred to Begleiter and Platz (1972) and Porjesz and Begleiter (1983).

For the past two decades in our laboratory, we have undertaken a systematic program of research utilizing a variety of evoked brain potential techniques to assess brain dysfunction in alcoholic patients. We recently recorded auditory brain stem potentials (BSPs) from hospitalized alcoholic patients who were abstinent from alcohol for 1 month (Begleiter et al. 1981). We observed that alcoholics manifested significant delays in latencies and central conduction velocities of peaks II–V, which represents activity at the pontine formation of the brain stem. These findings are similar to those reported by Squires et al. (1978a, b) in animals and man with acute doses of alcohol. The increase in neural transmission time may reflect a state of malnutrition or the process of demyelination, which has long been suspected in chronic alcoholics (Adams et al. 1959). Our study suggests that long-term alcohol abuse results in malnutrition and possible demyelination of auditory pathways beginning at the level of the pontine formation. Similar observations have recently been reported by other investigators (Rosenhamer and Silferskiold 1980; Chu and Squires 1980; Chu et al. 1982).

In an extensive study of 66 alcoholic patients, Chu et al. (1982) reported that alcoholics with cerebellar degeneration had the highest incidence of abnormal BSPs (83 percent). Furthermore, they found a high correlation between computerized tomography (CT) scan, cerebral atrophy, and BSP delays. The greater the number of neurological complications, the greater the likelihood of BSP deficits. The results of animal experiments (Chu et al. 1978) perhaps indicate that factors other than chronic alcohol exposure may be necessary to produce BSP abnormalities, as chronic alcohol ingestion in laboratory animals was not sufficient to cause BSP delays subsequent to withdrawal. These studies suggest that BSP aberrations in alcoholic patients may be the result of an interaction between alcohol and nutritional factors.

In addition to early far–field potentials, we have also been investigating long latency event–related brain potentials in alcoholic patients. We have examined ERPs in abstinent alcoholics who are hospitalized and medication–free. These ERP techniques require the subject to be engaged in a task, usually an information-processing activity. Each task is designed to examine deficits of a particular ERP component; these ERP components have been well documented in the ERP literature to vary in a predicted way under certain conditions in normal subjects. While we have examined a number of ERP components in alcoholic patients (for review, see Porjesz and Begleiter 1983), we will only briefly review our findings with the P3 component of the ERP. A P3 component is a late positive–going deflection, occurring at approximately 300–600 msec after a stimulus and obtained only to stimuli of significance (e.g., task–relevant target stimuli).

We have investigated the P3 component in alcoholics in a target–selection visual ERP paradigm (Porjesz et al. 1980). We

were interested in the ability of alcoholics both to differentiate between relevant and irrelevant events and to probability–match stimuli in terms of their frequency of occurrence. The stimuli were geometric shapes that differed in their frequency of occurrence. One rare geometric shape (e.g., a triangle) was designated target, and the subject was required to press a button only to that stimulus; this rare target stimulus would elicit large P3 components in normal subjects. Target and nontarget stimuli were alternated every other block, enabling the recording of ERPs to the same stimulus when it was a target or nontarget. We observed that P3 amplitudes were significantly decreased or absent in alcoholics to target stimuli under conditions optimal for eliciting large P3 voltages. This finding was most pronounced over parietal areas, where P3 amplitude is maximal at scalp (Simson et al. 1977a, b). The major ERP aberration manifested by alcoholics is the lack of differentiation between their responses to relevant and irrelevant inputs and the low voltages of their event–related activity.

Recent evidence suggests that the neural sources of the P3 component of the ERP may be other than neocortex and may implicate the hippocampus. One recent study investigating the neural generators of P3 with implanted electrodes in humans reported that P3 was maximum at subcortical loci (Wood et al. 1980). Similarly, Halgren and Associates (1980) completed a study with implanted electrodes in humans, in which they recorded large late potentials, which reversed in polarity in limbic structures. They postulate that the P3 component may be generated in hippocampus. While it is highly unlikely that one source generator may be solely responsible for the production of P3, it is nevertheless of great interest to note that parts of the limbic system may be involved. Thus, our results that alcoholic patients manifest low voltage or even absent P3 components under conditions designed to elicit maximum P3 component amplitudes may be indicative of hippocampal deficits. While these results do not rule out the contributions of other possible neuroanatomical sites, they emphasize the important role of limbic structures in generating the P3 component. The involvement of the hippocampus in chronic alcohol intake has been demonstrated in neuropathological and neurophysiological (Walker et al. 1981) studies in animals. Long–term ethanol consumption has been found to result in the loss of dendritic spines in the hippocampus of animals (Walker et al. 1980).

We have recently examined the relationship between electrophysiological deficits and structural deficits assessed with computerized tomography in alcoholic patients (Begleiter et al. 1980). We selected two groups of alcoholics who had been subjected to CT scans following 1 month of abstinence: those manifesting a high degree of widened cortical sulci (positive CT) and those without any evidence of widened cortical sulci (negative CT). Patients in the two groups did not differ with regard to age, edu-

cation, and drinking history (duration and amount). Alcoholics with enlarged cortical sulci (pos–CT) had significantly lower P3 voltages to target stimuli than did alcoholics with neuroadiological evidence of widened cortical sulci (neg–CT). It should be noted that both groups of alcoholics (pos–CT and neg–CT) manifested lower P3 amplitudes to target stimuli than did normal controls. Furthermore, both groups of alcoholics displayed similar P3 components to all categories of stimuli, regardless of task relevance. As alcoholics without signs of widened cortical sulci also manifested diminished P3 amplitudes when compared with 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 neurophysiological aberratons indicative of other brain (e.g., limbic system) deficits. The exact consequences of alcohol toxicity and withdrawal on brain damage or dysfunction and their interaction with other possible contributing factors such as premorbid brain dysfunction, abnormal thiamine metabolism, liver dysfunction, age of onset of alcohol abuse, nutrition, and other potential genetic factors are not currently understood.

We are now examining the possible reversibility of BSP and ERP deficits observed at 1 month in alcoholic patients. Abstinent, medication–free alcoholics are examined 1 month after admission and are reexamined while hospitalized, 4 months after admission. Our present BSP data indicate that, following 4 months of abstinence, we observe a significant improvement in the morphology of brain stem potentials, a shortening of latencies, and improved conduction velocity comparable with normal values. The relative roles of abstinence from alcohol and nutritional factors in so-called recovery remain to be determined.

While 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. We examined the possibility of reversibility of late component P3 deficits observed in abstinent alcoholics at 3 weeks and 4 months following abstinence. Interestingly, no reversibility 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, no improvement was noted in the differential enhancement of P3 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 P3 amplitudes. We have observed these P3 decrements in response to both auditory and visual target stimuli following 3 weeks and 4 months of abstinence. These results suggest that the P3 deficits may not be readily reversible in alcoholics; they may require very long abstinent periods for recovery to occur, or they may not be reversible at all even following prolonged abstinence.

We are currently investigating neurophysiological deficits in a group of nonhospitalized alcoholics sober from 3 to 10 years and have observed normal BSP latencies and conduction times. It should be noted that, while BSPs indicated no abnormality in this long–term abstinent group of alcoholics, P3 deficits were still present. Thus, it appears that some electrophysiological aberrations noted in alcoholics improve with prolonged abstinence (e.g., BSP), while other neurophysiological deficits do not change (e.g., P3).

It has generally been assumed that brain abnormalities observed in alcoholics are the consequences of the neurotoxic effects of alcohol, nutritional deficits, or an interaction of alcohol and nutrition–related factors. The possibility that the neurophysiological brain deficits in chronic alcoholics may in fact precede alcohol abuse has recently been suggested. There is increasing evidence that genetic factors may contribute to the risk of developing alcoholism. Specifically, sons of alcoholic fathers are four times more likely to develop alcoholism than sons of nonalcoholics, even when they are separated from their biological parents soon after birth (Goodwin 1979). Several elegant studies of male adoptees indicate that the biological rather than the adoptive parent is predictive of later drinking problems (Goodwin et al. 1973; Bohman et al. 1981; Cloninger et al. 1981).

Further evidence that a genetic predisposition is involved comes from a number of twin studies. These studies indicate that the concordance rate for alcohol abuse among identical twins is almost double the rate for fraternal twins (Kaij 1960). Taken together, these studies suggest that a genetic factor predisposing sons of alcoholic fathers to alcoholism may be involved. While most scientists agree that a combination of genetic and environmental factors is involved in the etiology of alcoholism, two fundamental questions must be investigated to shed further light on the etiology of this disease. (1) What is inherited, and in what fashion is it transmitted? (2) What is the nature of the interaction between biological and psychosocial factors that determines which individuals will manifest the disease?

These questions cannot be investigated until a specific technique becomes available to identify individuals who possess the genetic diathesis predisposing them to alcoholism. What is needed is a genetic marker that will identify those with the genetic predisposition. The genetic marker, a reliable indicator of the presence of a pathological gene or genes either associated or linked with a genetically influenced disorder, is ostensibly an observable manifestation of the genetic diathesis controlled or influenced by the pathologic genotype. The marker may be an antecedent factor that is etiologically related to the initiation of the disease, or it can be the result of the pathogenic gene that is not causally related to the disease. A valid genetic marker could be used as a valuable diagnostic tool. The advent of a reliable marker could

lead to the identification of a homogeneous subtype of alcoholism as well as provide fundamental clues about the pathophysiology of the disease. Furthermore, a marker would be of great importance in conducting longitudinal studies of high–risk individuals to assess the interaction between biological and psychosocial factors. Finally, the development of a biological marker would be of much help in identifying individuals early enough to permit preventive intervention. The search for a potential genetic marker must fulfill a number of criteria:

- Use of dependent variables known to be genetically influenced

- Variables present in specific diagnostic group (alcoholics)

- Variables relatively specific to the diagnostic category

- Occurring among first–degree relatives of patient at higher rate than that of normal population.

- Segregated with the illness in affected relatives

In recent years, we have undertaken a major program of research to investigate the possibility that sons of alcoholics manifest brain aberrations that antedate any exposure to alcohol. In order to study this problem, we are using a number of evoked potential techniques in boys between the ages of 6 and 18 and comparing electrophysiological recordings from sons of alcoholics (high risk—HR) and age, education, and socioeconomically matched sons of nonalcoholics (normal controls—NC). Children whose mothers abused alcohol at any time are excluded from the sample. We purposefully decided to study boys without any exposure to alcohol or other illicit drugs. The decision to exclude boys with limited exposure to alcohol was based on our wishes to avoid the confounding complex interaction between a potential genetic diathesis and the abused drug. The study of high–risk individuals not exposed to alcohol is quite important, because it provides an opportunity to examine correlates of the marker uncontaminated by the effects of alcohol or alcoholism.

We have recently reported (Begleiter et al. in press) the presence of P3 deficits in the ERPs obtained from subjects at high risk for alcoholism as compared with control subjects. Twenty-five sons of alcoholic fathers between the ages of 7 and 13, with a mean age of 11.9 (SD=2.1), were tested in this study. In each case, the father had received the exclusive diagnosis of alcoholism (DSM–III) and had at one time or another been in treatment for alcoholism. We excluded boys whose mothers had ingested alcohol during pregnancy or who drank excessively after giving birth. 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 NC 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 HR 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 (n=160). The target stimulus was an aerial view of the head with the nose and only one ear drawn in, rotated in four different positions: nose up and right ear (n=20), nose up and left ear (n=20), nose down and right ear (n=20), nose down and left ear (n=20). 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, respectively, was present in the display.

In the "easy" condition, the head was facing forward (nose up on the screen), and the left or right ear appeared directly on the side corresponding to the appropriate button. In the "difficult" condition, the head was facing back (nose down on the screen), and either the left or right ear appeared on the opposite side of the screen to the corresponding button. A total of 240 stimuli were randomly presented—160 nontargets and 80 targets (20 targets/ conditions). The stimuli were 25 msec in duration and subtended 2.9 degrees of arc; interstimulus intervals varied randomly between 2 and 4 seconds.

Reaction times for "easy" stimuli were significantly shorter than for "difficult" stimuli (p<.0001). There were no significant reaction time differences between groups. It is important to note that 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 Analyses 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 (see figures 1 and 2). Our results indicated that P3 was significantly larger in the NC group as compared with the HR group. This group difference was found to be significant at the parietal electrode (where P3 is maximum) for both the easy condition (p<.01) and the difficult condition (p<.002) (see figure 3). These findings are the first to indicate a significant difference in P3 amplitude between boys at high risk for alcoholism and normal control boys, without exposure to alcohol.

Differences in EEG have recently been reported between males with some family history of alcoholism and control subjects, in response to a challenge dose of alcohol (Pollack et al. 1983). Our
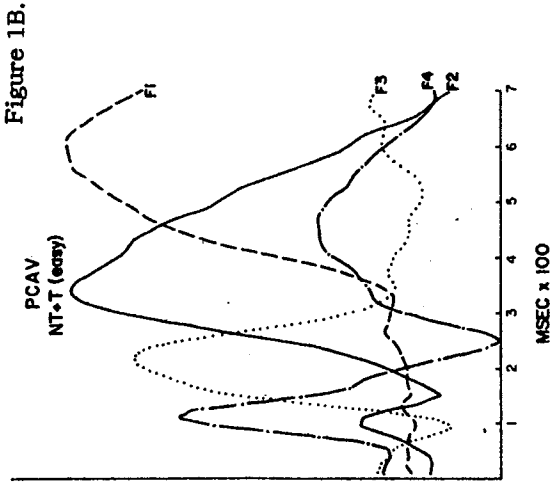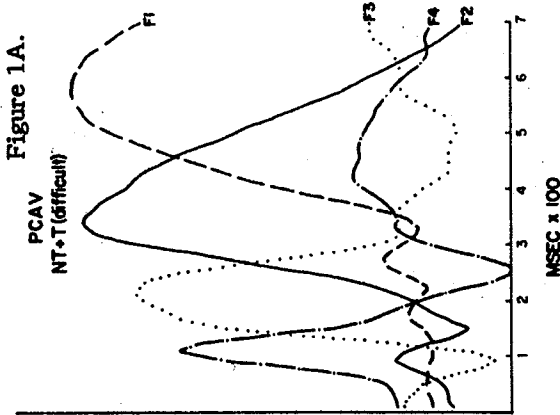
Figure 1A. Factor loadings of the first four factors obtained after Principal Component Analysis with Varimax Rotation (PCAV) for the difficult target and nontarget stimuli for both groups of subjects (normal control and high risk) at all four electrodes (Fz, Cz, Pz, Oz). Factor 1 is a rather broad component that peaks at 570.5 msec and represents the Slow-Wave (SW). Factor 2 peaks at 332.5 msecs and is maximum at the parietal lead; it represents the P3 or P300 component.

Figure 1B. Same as A for easy target and nontarget stimuli. Factor 1 (SW) peaks at 598.5 msec, and Factor 2 (P3) peaks at 332.5 msec.
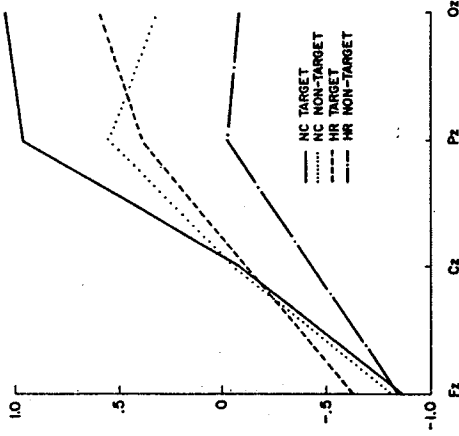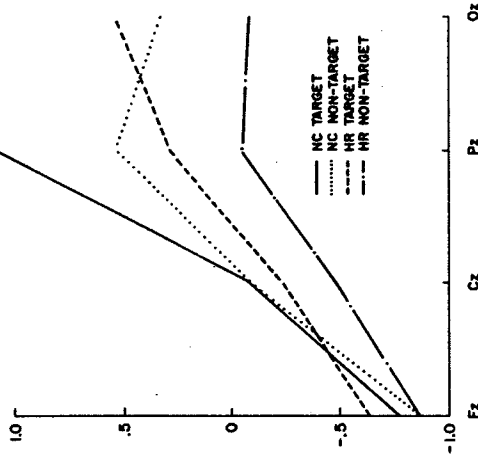
Figure 2A.

Figure 2B.

Figure 2A. Factor scores of Factor 2 (P3) plotted according to electrode (Fz, Cz, Pz, Oz) based on the easy target and nontarget PCAV. For each PCAV, the factor scores are illustrated for each group of subjects and stimulus condition, as follows: normal control target (NC target), normal control nontarget (NC nontarget), high-risk target (HR target), high-risk nontarget (HR nontarget).

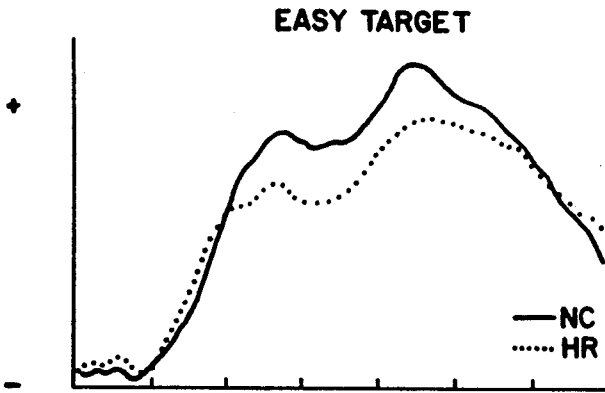Figure 2B. Same as A for difficult target and nontarget PCAV.

EASY TARGET

Figure 3A. Grand mean event–related potential (ERP) waveforms for the easy target at the parietal electrode (Pz) for the normal control (NC) and high–risk (HR) groups, respectively.
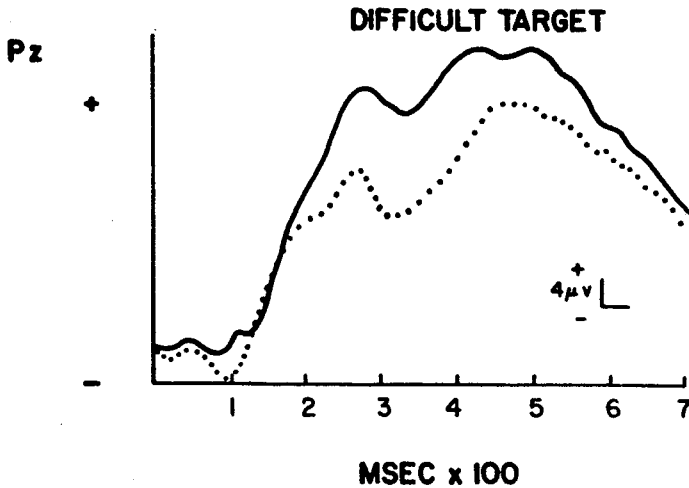
DIFFICULT TARGET

Pz

MSEC x 100

Figure 3B. Grand mean ERP waveforms for the difficult target at the parietal electrode (Pz) for the normal control (NC) and high–risk (HR) groups.

findings are particularly interesting, since they were obtained without the use of alcohol. A recent evoked potential study at the Salk Institute (Elmasian et al. 1982) found that males with a fam–

ily history of alcoholism respond differently to challenge doses of both placebo and alcohol when compared with males without a family history of alcoholism. P3 amplitudes and latencies were found to differentiate between the two groups.

It is interesting to note that the P3 deficits we have observed in abstinent alcohol patients are present also in some boys at high risk for alcoholism. In light of the similarity in P3 findings between abstinent alcoholics and boys at high risk for alcoholism, we have recently undertaken to examine brainstem transmission time in high-risk individuals. We have observed brainstem abnormalities in abstinent alcoholics (Begleiter et al. 1981).

In this study (Begleiter et al. 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 (NC) were boys who were matched for socioeconomic status, age, and school grade to the high-risk (HR) boys. The NC group had a mean age of 12.4 (SD=2.3). As in our previous neurophysiological study of high-risk individuals, the inclusion and exclusion criteria were identicial. Again, we included boys without exposure to alcohol or other illicit drug.

Auditory brainstem potentials were recorded in both groups of children in a manner identical to that used in our study of brainstem potentials in chronic alcoholics (Begleiter et al. 1981). Auditory brainstem potentials were evoked monaurally with the use of 2,000 clicks. Each click (0.5 msec duration) was generated by a Grass click-tone generator and presented through earphones (TDH-39) at a rate of 10 clicks per second. Each ear was tested randomlyacross all subjects. Stimulus intensity was 70 db above threshold. Monopolar recordings were obtained between a vertex electrode and the ipsilateral earlobe, with an electrode on the forehead serving as the ground. The potentials were amplified 100,000 times and were subjected to a digital filter with a band-pass of 100 Hz to 2 KHz (Boston and Ainslie 1980). The computer sampled the electrical activity at a rate of 40 KHz for 10 msec following the click. The initiation of sampling was delayed by 1 msec in order to eliminate the stimulus artifact from the display. We measured the latency of the first five positive peaks including the interpeak latencies between peak I and each successive peak. The interpeak latency between peaks I and V is inversely related to the conduction velocity in the ascending pontine segment of the auditory pathway and is an index of brainstem transmission time (BTT).

Our findings indicate that the auditory brainstem potentials obtained from sons of alcoholics do not differ significantly from those obtained from matched control subjects. Both the individual peak latencies and the brainstem transmission time are similar in the high-risk individuals and normal controls (see figure 4). The lack of significant difference in brainstem potentials between HR and NC subjects is interesting in light of our observed difference
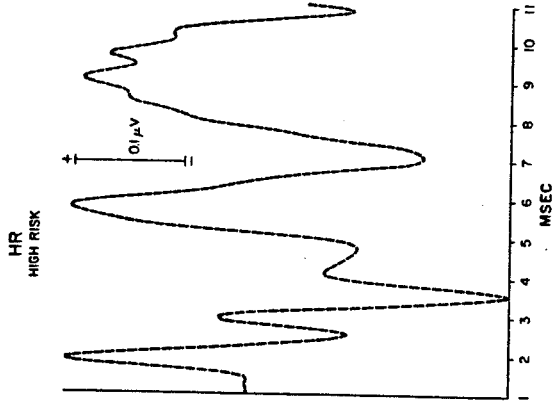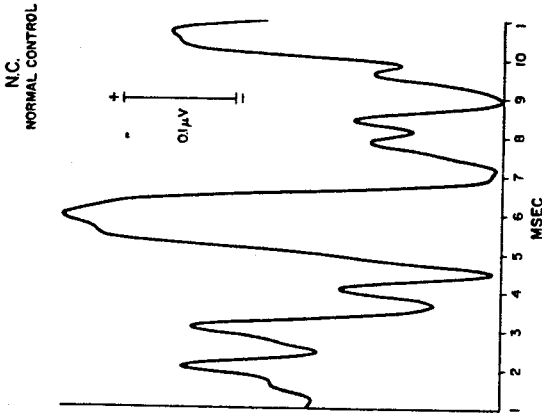
figure 4 – wide format

Figure 4A. Auditory brainstem potential obtained from normal control (NC) subjects.

Figure 4B. Auditory brainstem potential from high–risk (HR) boys.

in P3 between HR and NC subjects. The present findings indicate that, while P3 deficits may antecede the development of alcoholism in some high–risk individuals, the brainstem deficits we have observed in abstinent alcoholics are alcohol–related changes. Our current findings indicate that the CNS deficits that may be present in HR subjects are not general or nonspecific but may be restricted to specific CNS systems.

The ability to utilize sophisticated neurophysiological tools in assessing brain dysfunction in abstinent alcoholics and individuals at risk for alcoholism should prove most valuable in separating the deleterious effects of alcohol on CNS from brain deficits that 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 search for and identification of a possible genetic marker. The search for a possible cluster of neurophysiological deficits in children at high risk for alcoholism is now underway at our laboratory.

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