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Neurophysiological Dysfunction in Alcoholism

H. Begleiter and B. Porjesz

)epartment of Psychiatry, State University of New York, Health Science Center at Brooklyn, Brooklyn, New York 11203

The relative inaccessibility of the living human brain to direct neurobiological crutiny has made it difficult to examine brain dysfunction in alcoholism. Whereas t has long been apparent that the human brain is very susceptible to both the ıcute and chronic effects of alcohol, it is only recently, with the development of ophisticated technology, that these effects can be studied in vivo. The development)f advanced computer technology has made it possible to investigate functional)rain deficits in alcoholics with noninvasive Evoked Brain Potential (EP) techniques. These evoked brain potential techniques permit an examination of more subtle 'orms of brain damage and/or dysfunction that had heretofore been unobtainable. The event-related potential (ERP) techniques offer a unique approach for assessing evel of brain functioning, as they permit the simultaneous observation of electro-)hysiology and cognition.

An event-related potential is obtained by recording the time-locked brain electrical ıctivity 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 (event-related potentials) from the background random "noise," which cancels 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 organ to neocortex) can be assessed.

ERP techniques have proven to be very useful in indexing electrophysiological concomitants of complex cognitive tasks (21,22,38). 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 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

Evoked potential 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 (11) and prolongations in conduction velocities of the brain stem potential (BSP) (20, 84,85). Chronic alcohol intake is accompanied by EP amplitude reductions (2,66) and BSP delays that are less pronounced when tolerance develops (20,84,85,98). 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 (2,3,4,20,39,84,85). Finally, long-term abstinence is marked by decreased EP amplitudes (hyporeactivity) and prolonged BSP latencies and slower conduction velocities (6,63). 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 evoked potential techniques.

Auditory Brain Stem Potentials (BSPs)

We have recently recorded auditory BSPs from hospitalized alcoholics who were abstinent from alcohol for one month (6). With this technique it is now possible to investigate subcortical brain functioning with a noninvasive scalp electrode (40,41,81). 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 (14,40,48,86,87,88). 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 (25).

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 (84) and humans (85). 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 (1) and has been observed in rats chronically exposed to alcohol (52). Similar results have recently been reported in neurologically impaired alcoholics (18,19, 34,54,75), and in neurologically intact alcoholics (17). 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 (36). 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 different BSP waveforms than other alcoholics. Furthermore, length of drinking history does not seem to correlate with BSP delay; in fact, alcoholics with relatively short heavy drinking histories (8 years) but evidence of nutritional deficits manifested greater BSP aberrations than alcoholics with long drinking histories (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 (20) 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 was not sufficient to cause BSP delays after withdrawal.

Event-Related Brain Potentials (ERPs)

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 are abstinent for approximately one 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 (22,38).

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 Nl component of the ERP (60), a component that occurs around 100 msec. The Nl 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 (37,38,56). The patient was presented with a sequence of randomized single flashes and clicks with rarely occurring double flashes and clicks interspersed among them. He was 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; these frequent single flashes elicit Nl components that are differentially enhanced in the relevant channel (stimulus modality).

The results indicated that abstinent alcoholics manifested abnormally reduced late component (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 (50,59,69). 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 (37,38), control subjects in our study manifested significantly enhanced Nl components to stimuli in the relevant as compared with the irrelevant modality; however, alcoholics maintained the same low amplitude of Nl 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 P3 component of the ERP to examine brain dysfunction in alcoholics, with many different experimental paradigms. The P3 or P300 component is a large, positive deflection that occurs approximately 300 to 500 milliseconds after the stimulus. It can be elicited only under certain rather specific conditions related to the "subjective significance" of a stimulus, namely, task relevance (89), unpredictability (22), infrequency (92), as well as by motivational factors (8). The characteristics of P3 are unrelated to stimulus parameters, and can even be elicited in the absence of an expected stimulus (emitted potentials) (46). 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 (78,79,80).

In one study in our laboratory, we investigated the P3 component with a visual target-selection paradigm (67). The target-selection paradigm is most frequently used to 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 Nl components, but no P3, whereas rare target stimuli elicit both Nl and P3 components. In our study (67) 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 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 (rarely occurring task irrelevant random shapes) stimuli.

Despite the fact that all stimuli were in the relevant channel, we found that the N1 amplitudes were significantly depressed in alcoholics to all stimuli, to levels comparable to an irrelevant stimulus modality. As in our bimodal study (60), this suggests that "sensory-filtering" mechanisms are impaired in chronic alcoholics. Furthermore, we found that P3 amplitudes were significantly reduced or absent in alcoholic patients to rare target stimuli under conditions optimal for eliciting large P3s (22). This finding was most pronounced over parietal areas, where P3 amplitude is maximal at scalp (71,79,80). Furthermore, although controls manifested differentially enhanced late 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. Thus, 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. This seems to suggest underlying brain dysfunction that impairs "sensory-filtering" and "probability-matching" processes.

Despite its maximal amplitude over parietal areas at scalp, recent evidence suggests that the neural origins of P3 may be subcortical, and implicate the amygdala and hippocampus. One recent study investigating the neural origins of P3 with implanted electrodes in humans reported that P3 was maximum at subcortical loci (96). Similarly, Halgren et al. (35) 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.

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 deficits. Whereas these results do not rule out the contributions of cortical 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 (4,5,70,94,95). Long-term ethanol consumption has been found to result in the loss of dendritic spines in mouse (70) and rat (70) 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 (4).

We were interested in determining the relationship between electrophysiological deficits and structural deficits assessed with computerized tomography (CT-Scan) in alcoholics (5). We selected two groups of alcoholics who had been subjected to CT-Scans following one 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 (67). Alcoholics with enlarged cortical sulci (Pos-CT) had significantly reduced (or absent) P3 amplitudes to target stimuli as compared with 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.

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 electrophysiological aberrations indicative of other brain (e.g., limbic system) deficits. Often the neocortical deficits in chronic alcoholics are emphasized whereas 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 in neocortical areas.

We have recently completed a study examining the N2 or N200 component of the ERP in abstinent alcoholics (61,62,64). 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 N2 can be taken as an early index of stimulus evaluation time (68); the more difficult discrimination, the longer the latency of N2 (30,73,91). The N200 component is a better index of stimulus evaluation t'.= than the reaction time (RT) because it is not confounded by the motor response. The reaction time 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 (10,90,93), these studies cannot determine which aspect(s) of information processing are slower in alcoholics.

We were interested in specifically examining the speed of stimulus evaluation in chronic alcoholics, using the N2 component of the ERP as an index. Therefore, we designed a RT study involving easy and difficult line orientation discriminations. This visuo-spatial RT design enabled us to investigate the relationship between difficulty of discrimination, N2 latency, P3 characteristics, and RT in abstinent chronic alcoholics. ERPs were obtained to frequent nontargets (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 with the easy discrimination. However, 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 find the discrimination task more difficult, and hence need 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 alcoholics need proportionately more time to make an easy discrimination (vertical

from horizontal) when compared with 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 with 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. Although 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 degree of stimulus deviance in normal subjects (53).

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 missing target stimuli, although these results were not significant. This response pattern indicates that speed is stressed over accuracy (47), implying that alcoholics adopt different response strategies from controls—stressing speed over accuracy. These results suggest a lack of inhibition in chronic alcoholics reflected by their apparent inability to withhold responding until certainty of accuracy or correctness has been established.

In addition to these latency results, we found that alcoholics had significantly depressed 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 with the 3-degree target in the control but not the alcoholic subjects. This result is predicted by many ERP studies that have demonstrated that the more deviant a rare stimulus is from the background (the more easily discriminable it is), the larger the P3 amplitude (28,42,72,76,91). 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. Furthermore, although controls manifest significant target/nontarget P3 measures, alcoholics do not.

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; rather, they 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 dysfunction: the delay in N2 latency suggests that the template for comparison is not as readily accessible in alcoholics, whereas the low P3 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 one month of abstinence and following 4 months of continued abstinence in the same hospitalized alcoholics (58,65). Preliminary data following four 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 brainstem latencies caused by aberrant fluidizing effects on the membranes that may result in edema. It should be noted that edema resulting from osmotic stress can lead to demyelination (26,27,45,49,97).

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

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 (58,65). We examined the possibility of reversibility of late component P3 deficits in abstinent alcoholics following three weeks and four months of abstinence. Interestingly, no improvement in ERP morphology or late component amplitude was noted following four 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. Thus, even following four 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 three weeks and four months of abstinence in a bimodal target-selection study. These results suggest that the P3 deficits may not be reversible, or may perhaps reverse much more slowly following very long abstinence periods. It is even possible that these P3 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 from three to ten years, and have found they manifest normal BSPs. This suggests that perhaps four months is not a long enough interval to investigate reversibility of brain dysfunction following years of heavy drinking. However, these long-term abstinent alcoholics (three years) 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. Although the issue of reversibility is still unresolved, the data seem to indicate slow reversibility of BSP deficits with prolonged abstinence, However, as P3 deficits were still observed following the same prolonged sobriety period (three years), the data suggest no recovery of P3 deficits following long-term abstinence. Thus it seems that some electrophysiological aberrations observed in chronic alcoholics improve with prolonged abstinence whereas 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 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 nutritional-related factors. The possibility that these brain deficits may in fact precede alcohol abuse has been suggested only 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 (31,33), 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 (12,15,16,32,33,77). Furthermore, the concordance rate for alcohol abuse among identical twins is almost double the rate for fraternal twins (44); patterns of alcohol consumption have also been found to be highly concordant among identical twins (43,51,55) 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(s) 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 (23).

We have recently undertaken a major project to investigate the possibility that sons of male alcoholics manifest differences in evoked brain potentials 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 to rule out the contribution of the Fetal Alcohol Syndrome (FAS).

In one ERP study (7) we examined the P3 component in boys between the ages of 7 and 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 and age to the high-risk (HR) subjects. The NC group had a mean age of 12.5 years (S.D. = $\pm$ 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. 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 drawn in. 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. 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.

Reaction times for "easy" stimuli were significantly shorter than for "difficult" stimuli ($p < 0.0001$); 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" ($p < 0.001$) and "difficult" stimuli ($p < 0.001$). The entire raw data set was subjected to a Principal Component Analysis with Varimax Rotation using the covariance matrix (PCAV). Basic 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 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 with the NC group. This group difference was found to be significant at the parietal electrode (where P3 is maximum) for both the easy

condition ($p < 0.01$) and the difficult condition ($p < 0.002$). 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 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 (57) and ERP (24) recordings. In a study conducted at the Salk Institute, Elmasian et al. (24) found that male college students with family histories of alcoholism manifested different ERPs to challenge doses of both placebo and alcohol, when compared with 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 underway 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 P3 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 brainstem abnormalities in abstinent alcoholics (6), we decided to record brainstem potentials (BSP) in high-risk boys.

In this study (9) 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.= $\pm$ 2.1). The 23 normal control subjects (NC) were boys matched for socioeconomic status, age, and education to the high-risk (HR) boys. The NC group had a mean age of 12.4 (S.D. = $\pm$ 2.3). The inclusion and exclusion criteria were identical to those previously described for the P3 study. Again, we included only boys without prior exposure to alcohol or 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 brainstem potentials obtained from sons of alcoholic fathers (HR) and those obtained from matched control (NC) 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 although P3 deficits may antecede 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 obtained by our findings that the BSP abnormalities observed in abstinent alcoholics seem to "recover" with prolonged abstinence, whereas the P3 deficits do not.

CONCLUSION

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 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 were predisposed to drink alcohol or found it to be aversive (74). Furthermore, differences in neurophysiological responses to alcohol have been reported in different genetic rat strains (82). Humans have also been found to differ in their responsiveness to alcohol; for example, augmenting/reducing (83,13), family history for alcoholism (24,57) flushers/nonflushers (29). 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 (29). It is possible that the low P3 amplitudes we observe in young sons of alcoholics represent a vulnerability marker that may become apparent only 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 underway 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 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 identification of possible genetic marker(s). The search for a possible cluster of neurophysiological deficits in children at high risk for alcoholism is presently underway in our laboratory.

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DISCUSSION

Dr. Joseph Zubin: We should be very grateful to Dr. Begleiter for demonstrating that P300 can be useful in understanding other disorders besides schizophrenia, where it was first discovered. I have never seen as direct a connection between the mind and the brain as exists with P300. It is strange that such things as uncertainty about the next stimulus should be reflected in P300.

P300 becomes a measure of the degree of uncertainty experienced in watching for a stimulus. It also reflects the value of the stimulus. For example, if you bet a dollar or if you bet only 50 cents on the identity of successive stimuli, whether you win or lose, there is a difference in the size of the amplitude of P300. With P300 we have opened up a window on the brain that tells us how the mind is functioning.

We discovered P300 by sheer accident. We had been wondering what happens in the brain when two identical or different stimuli are presented one after the other. If the stimuli are in different modalities, there is a longer latency in the reaction time to the second stimulus. However, if the stimuli are in the same modality, then you don't get that latency in reaction time to the second stimulus. One day Sam Sutton said to me, "We have got the CAT machine working averaging brain waves, so give us an experiment to do." The CT averager is what made the discovery of P300 possible. Imagine what would be involved if you had to measure these tracings by hand, since each one represents a hundred readings. I naively said, "Well, could you find out what the brain is doing while that latency in reaction time is occurring?" Out of that, the P300 was born. When we first saw the P300, I didn't believe it, but Sam had faith in it, and we went at it until finally we demonstrated it really exists. Now, of course, people see P300 everywhere, over the entire world, whenever the proper conditions apply.

Did you intimate that the P300 effect in alcoholics disappears in time; in other words, that it is an episode marker that occurs only during the alcoholic episodes, or does it persist?

Dr. Begleiter: What appears to be the case, both in our laboratory and in many others, is that the brainstem effects disappear with time. But the P300 effect, at least the late positive component effect, appears to be quite stable. If it is deficient initially, we find it deficient subsequently, some four months after retest. It appears to be a stable measure, and indeed we see it in long-term abstinent alcoholics, even though we did not test them initially. Of course, we cannot talk about test/retest, but it is present enough so that when we average the data, or do mean comparisons, we get significant differences.

Dr. Hans Huessy: Can these findings be distinguished from the findings reported in relationship to attention deficit disorder children?

Dr. Begleiter: Yes, they can. We have another control group, made up of what were then called hyperactive children and who would now be diagnosed as ADD. If one analyzes the data in a more sophisticated way than what I have shown you, namely, not looking at the principal component analysis or at amplitudes or latencies, but at wave-form analysis, there are some strikingly significant differences between normal children, children at high risk for alcoholism, and ADD children. One can discriminate these groups quite well.

Dr. Deborah Hasin: How specific is this effect to alcoholism? Is it also found in children of subjects with other psychiatric disorders?

Dr. Begleiter: It was not specific at all, and it has been reported in children with other conditions. For instance, it is typically found in schizophrenic patients. I personally am not disturbed by the lack of specificity, since I never intended, nor do I believe, that anyone will find a biological phenomenon that is totally specific to predisposition for alcoholism. I think what we are hoping to find is a cluster of factors. I do think this finding may be part of a cluster, and we need to look further to find the rest of the cluster.

Dr. David Janowsky: Do you know of any pharmacologic challenges or events that cause parallels to the phenomena you mentioned?

Dr. Begleiter: There are. You will be fascinated by the answer because of your interest in the acetylcholine system. Cholinergic drugs modulate the P300 very nicely; antagonists knock it down, and agonists bring it back up. These are unreported data, but, indeed, these findings appear to be the case not only in animals but also in people.

Dr. Janowsky: I was asking a general question, but it may relate to some findings that we in San Diego noticed during Marc Schuckit's Alcohol Research Center investigations. We found that when we gave physostigmine to our primary alcoholic patients, in contrast

with nonalcoholics and alcoholics with a true affective disorder component to their syndrome, we saw a blunting of the physostigmine response. How might this relate to your observations?

Dr. Begleiter: There are some physostigmine data, unpublished but reported in the Neurology Department of the University of Florida at Gainesville, that show that the antagonists knock down the P300, and the agonists bring it right back up.

Dr. Robin Murray: You split the first group of alcoholics into those with and without CAT scan abnormalities. In the abstinent alcoholics, obviously some patients will still show CAT scan changes. Did you again split the abstinent alcoholics into those with normal and abnormal CAT scans?

Dr. Begleiter: Yes, we did. We reported these findings at a conference that took place in Stockholm about two or three years ago.

Dr. Sheila Blume: Did you find subgroups, either of adult alcoholics or sons of alcoholic fathers, that showed perfectly normal P300s?

Dr. Begleiter: We did. Among high-risk children, there was a large proportion of wonderful late positive complexes. I think it is important to mention that in our sample, only 35% of the high-risk children showed that deficit. The other 65% appeared to be relatively normal, if one classifies as normal or abnormal based on the score and departure from the mean. This was a rather crude way of classifying, but nevertheless we did see that approximately 35% had a P300 voltage abnormality.

Many alcoholics have perfectly normal P300s. Indeed, there is a wide range of P300 voltage, all the way from totally absent to perfectly normal.

Dr. Zubin: It need not be surprising that not all of the offspring show the P300, because only 50 percent of the offspring should carry the genetic transmission. You would expect quite a proportion not to show it.

Dr. Begleiter: We are currently doing a study in collaboration with Dr. Reich. We are sending him pedigree data, and he is attempting to quantify the degree of risk, looking at pedigree and other psychosocial data. What we hope to do is correlate our electrophysiological deficits with that index that he will derive from pedigree data.

Dr. Robert Rose: Would you be willing to speculate for us a bit about what you think the abnormality is? Early on, you talked about generators, and you have some concepts as to what may be the neurophysiological abnormality that is being expressed by this diminution in the magnitude of P300.

Dr. Begleiter: I really don't know. There are some interesting studies underway; two groups of investigators are doing this type of study in humans—one at UCLA and another at Yale. Similar studies are being done in animals—rats, cats, and monkeys.

There is a good deal of agreement. It appears that the hippocampus in a very limited way is involved in P300 production. Some new data indicate that the frontal lobes may be involved. The reason I think it is too early to speculate is that we are definitely going to see multiple generators, and at this point we are looking only at single generators. What needs to be done, once we have some idea about single generators, is to look at multiple generators. Those studies can be carried out only in animals, in monkeys, and these monkey studies are just in their infancy. So I think that within the next few years we will know a great deal more about the neurophysiology of these latent potentials, but right now the information is very, very limited.

Dr. Jerome Jaffe: When you were asking these young people if they ever had a sip of beer, did you record anything about their personalities or give any kind of test? If so, did the 35% who had abnormalities of P300 appear in any way different from the 65% who had normal P300?

Dr. Begleiter: We didn't see any differences. I should mention that the children and the mothers were interviewed at the same time, but by two different interviewers. If either one of the two reported a possible exposure to alcohol, that child was automatically taken out; we had to have agreement between mother and child. We did not find anything either spectacular or unusual.