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Human Brain Electrophysiology and Alcoholism

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1. INTRODUCTION

Chronic alcoholism is characteristically associated with a broad spectrum of brain disturbances ranging from the severe symptoms of the Wernicke–Korsakoff syndrome[1,2] to the more subtle, but nonetheless significant, cognitive disturbances characteristic of the majority of alcoholic patients. In some alcoholics the brain damage is so severe that it renders the individual ineffective as a meaningful member of society. Less clinically apparent forms of brain damage in alcoholics have been suspected for decades but ignored, because sensitive techniques required for their detection in vivo were unavailable. Significantly, brain dysfunction of a subclinical severity may impair the ability of affected individuals to either reduce their intake or abstain from alcohol. Moreover, by impairing social functioning, it may also account for such phenomena as "loss of control" over drinking when it occurs.

The etiology of alcohol-related brain damage is not entirely known. There is increasing evidence that the ingestion of alcohol results in central nervous system (CNS) functional changes during acute and chronic intoxication, as well as during periods of alcohol withdrawal. In some cases, these CNS changes are quite long-lasting, and it is uncertain whether they reverse completely even after prolonged abstinence. Although it is recognized that the brain is quite susceptible to the deleterious effects of ethyl alcohol, the exact consequences of ethanol (or

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acetaldehyde) toxicity and withdrawal phenomena on the CNS, and their interaction with repeated patterns of alcohol exposure, are at the present not well understood. The role of other possible contributing factors such as premorbid brain dysfunction, genetic factors, abnormal thiamine metabolism, liver pathology, age of onset of alcohol abuse, and nutrition is as yet largely unknown.

Some of these issues are being investigated presently in animals. Thus, for example, a number of laboratories are examining the effects of acute and chronic alcohol on neurophysiologic functioning.[3–8] Although animal studies are necessary for advancing our knowledge about alcohol-related brain disturbances, they are not sufficient to elucidate the range of CNS dysfunctions associated with alcoholism in the human. Moreover, inasmuch as alcoholism is a uniquely human condition, it is imperative to conduct investigations of brain dysfunction and concomitant clinical symptoms in alcoholic patients. The relative inaccessibility of the living human brain to direct study, however, makes it difficult to study alcohol-related brain dysfunction in man.

The recent development of computer technology has made it possible to investigate structural [computerized tomography (CT)] and functional (evoked potential) brain deficits in chronic alcoholics using noninvasive techniques. These techniques permit an examination of the more subtle forms of brain damage and/or dysfunction that heretofore had been unobtainable.

The assessment of structural brain damage in chronic alcoholics has been greatly facilitated by the use of the CT scan. The studies conducted so far have revealed widened cortical sulci, particularly in the frontal areas.[9–15] This technique is limited, however, because it visualizes morphologic changes in certain brain areas (e.g., cerebral cortex) better than it does in other areas (e.g., brain stem). Furthermore, the CT scan provides a static picture of gross brain morphology, without providing information about the underlying pathophysiology. The relationship between brain damage (as visualized on the CT scan) and level of brain functioning (as assessed by neuropsychologic tests) is, at best, modest.[16] Although neuropsychologic tests are useful for assessing cognitive deficits in chronic alcoholics, their utility for studying brain functioning is limited because they *infer* brain pathology from behavioral measurements. Moreover, the specific behavioral deficits (e.g., abstracting impairment) found in alcoholics may well be the product of several different complex neurophysiologic processes or neuropathologic problems acting in concert.

With the advent of computers and the development of sophisticated mathematical techniques, it is now possible to obtain objective quantitative neurophysiologic data from the analysis of *evoked brain potentials*. The evoked potential (EP) or event-related potential (ERP) technique offers a unique approach for assessing multiple levels of brain functioning because it permits the simultaneous investigation of electrophysiology and cognition. Quantitative measurements of salient features extracted from EP or ERP recordings reflect various

aspects of brain function related to integrative processes of the brain, as well as the functional integrity of different neuroanatomic systems. These powerful EP techniques occupy the interface between cellular neurobiology and the behavioral sciences.

An EP is obtained by recording the time-locked brain electrical activity following the delivery of a discrete stimulus via a given sensory modality (e.g., auditory, visual). The neuroelectric activity that is time-locked to the stimulus (signal) is elicited with each stimulus presentation, whereas the background "noise" in which it is embedded is ignored. Signal-averaging techniques make it possible to extract the time-locked neuroelectric signal (EP) from the background random "noise" which essentially cancels out using these procedures. These time-locked signals, depending on the stimulation properties and recording sites chosen, represent activity at neural generators from the peripheral end organ to the higher integrative centers of the brain. Thus, with the use of these sophisticated techniques, the functional integrity of the brain (from the peripheral end organ to neocortex) can be assessed in vivo.

ERP techniques have proven to be very useful for indexing the electrophysiologic concomitants of cognitive performance. ERPs have an advantage over neuropsychologic tests in that they can be recorded in conjunction with behavior, and even when no behavioral response is required, they can be recorded and related to both attended and unattended stimuli. Thus, ERP techniques are very sensitive indices of the functional integrity of the brain. They differ from the CT scan in that they reflect subtle dynamic moment-to-moment changes in brain functioning elicited while the brain is being challenged, rather than reflecting static gross brain damage. Significantly, ERP aberrations are often observed in the absence of brain damage visualized by the CT scan.

As might be expected, recording brain electrical activity has proven to provide a sensitive measure of alcohol-related effects, namely, alcoholization, tolerance, withdrawal, and long-term brain dysfunction.[17,18] Alcoholization is characterized by marked depressions in EP amplitudes[19] and prolonged conduction velocities of the brain stem potential (BSP).[20–22] Chronic alcohol intake is accompanied by EP amplitude reductions and BSP delays which are less pronounced after tolerance has developed.[18,20–24] These techniques are sensitive to withdrawal phenomena as well. Withdrawal is characterized by increased EP voltages and extremely shortened BSP latencies indicative of an underlying CNS hyperexcitability.[5,17,20–23] Finally, long-term abstinence is marked by decreased EP amplitudes (hyporeactivity) and abnormally prolonged BSP latencies and conduction velocities.[15]

For an extensive review of the effects of alcohol on electroencephalographic activity, the reader is referred to Begleiter and Platz.[25] The present chapter reviews the findings on brain dysfunction in chronic alcoholics as assessed using EP techniques. The discussion will be divided into two major sections. The first

section examines the effects of acute doses of alcohol on brain functioning in healthy nonalcoholics in whom various EP techniques have been employed. The second section addresses the electrophysiologic assessment of brain dysfunction in chronic alcoholics. The latter section is further subdivided into three subtopics, each dealing with different postwithdrawal periods following alcohol abuse, namely, short-term abstinence (withdrawal), long-term abstinence (subacute withdrawal), and recovery. Each section and subsection will be further subdivided according to the EP technique used to assess brain functioning, these being (1) *brain stem potential* (BSP), (2) *sensory evoked potential* (EP), and (3) *event-related potential* (ERP).

2. ACUTE ALCOHOLIZATION

The effects of acute doses of alcohol on normal brain functioning have been investigated with EPs. In these studies, the EP has been found to be useful in determining the differential responsivities of different brain loci to ethanol effects. Perhaps by elucidating the sites of action of acute alcohol exposure in the brain, loci of brain dysfunction resulting from chronic alcohol abuse can be suggested.

2.1. Auditory BSP

Since the advent of the auditory BSP technique, it has become possible to record subcortical brain functioning using noninvasive scalp electrodes.[26–28] These "far-field" potentials consist of seven time-locked positive waves. Each wave is presumed to reflect activity at different sites ranging from the auditory nerve to the medial geniculate.[27,29–33] The latency of each peak, as well as "central conduction time" (the latency of each peak with respect to peak I), accurately localizes the site of pathology between the peripheral end organ and the brain stem. Most attention has focused on the time interval between the first peak and peak V (inferior colliculus) as a measure of transmission time.[34]

The acute administration of alcohol to animals has been found to delay the central conduction time of peaks III to V and VII,[20–22] but not the early peaks (I and II). Similarly, increased delays of peaks II to VII,[35] III to VII,[36] and IV to VII,[21] but not peak I, have been reported in healthy human subjects administered acute doses of alcohol. This seems to indicate that alcohol affects conduction time in more central structures (beginning at the level of the medulla), but not the auditory end organ. These later waves have been reported to be delayed sooner after alcohol ingestion than are the earlier peaks.[21] Interestingly, only the latency of wave VI has been reported to be related directly to dose of

alcohol, suggesting that the medial geniculate is particularly sensitive to blood alcohol concentrations.

An interesting study conducted in Japan[36] reported that subjects who manifested facial "flushing" in response to alcohol displayed significantly larger shifts in the latencies of peaks III, V, and VII than did "nonflushers," despite a lack of difference between the two groups in terms of blood alcohol levels. The investigators postulated that the group differences were due to differential blood acetaldehyde levels; however, no measurements of acetaldehyde were obtained.

Recent evidence indicates that even a moderate dose of alcohol (0.5 g/kg) given acutely is sufficient to produce shortened BSP latencies of peaks VI and VII,[35] beginning as early as 3.75 hr after alcohol administration. The decreased latencies produced by ethanol persist longer than do the initial alcohol-induced increases and are still apparent at the end of the test session (6.75 hr post-ethanol). These findings suggest that withdrawal from even a moderate dose of alcohol given acutely can elicit CNS hyperexcitability. As will be discussed in a later section, withdrawal-related BSP decreases have been reported after chronic alcoholization of rats.[22]

There is still some controversy as to whether the BSP latency changes produced by ethanol are the result of alcohol-induced hypothermia or alcohol per se. Many studies have demonstrated that changes in brain temperature affect BSP latencies.[37–40] Thus, Jones et al.[41] have reported no temperature-independent alcohol effects on BSP latencies recorded in cats. Only when temperature changes exceed 0.5°C were BSP latency shifts noted. Conversely, a recent study by Church and Williams[35] found that temperature changes were not responsible for alcohol-induced BSP delays in humans. Their results demonstrated that the maximum temperature change found in their human subjects after alcohol ingestion (-0.3°C) was insufficient to produce a shift in BSP latency. Furthermore, they argued that Jones et al.[41] had investigated this problem at an inappropriate time frame (>2 hr postalcoholization). On the basis of the limited available findings, the recent evidence is inconclusive with respect to whether brain temperature changes are necessarily involved in mediating the BSP latency shifts associated with alcohol exposure.

2.2 Sensory EP (P1–N1–P2)

Average EPs recorded to repetitive stimuli of any sensory modality have a characteristic positive–negative–positive (P1–N1–P2) wave form that occurs approximately 60 to 250 msec after the stimulus is applied. The recorded wave form is somewhat arbitrarily divided into "early" components (<100 msec) and "late" components (>100 msec) depending on their timing after the stimulus. The early components are related more to the characteristics of the stimulus

(e.g., intensity) whereas the later components appear to reflect psychologic processes (e.g., habituation).

During the past decade and a half, the effects of acute doses of alcohol on scalp recorded human sensory EPs have been investigated in an effort to determine if there are any specific neurophysiologic reactions to alcohol. To this end, EPs have been recorded after acute alcohol administration to humans using different sensory modalities, namely, auditory,[36,42–49] somatosensory,[50–53] and visual[50,54–60] (and A. Pfefferbaum et al., personal communication, 1977).

All the studies concur that alcohol ingestion primarily produces a marked depression in the late (N1–P1) components occurring after 100 msec[36,46,52,54,56–59] (and A. Pfefferbaum et al., personal communication, 1977). Although the late EP components are reduced consistently, the early components (<100 msec) are relatively resistant to the depressant effects of alcohol regardless of the sensory modality used.[46,50,52,56,57]

A reduction in average EP amplitude can either be the result of increased latency jitter or be a reflection of decreases in each of the EPs that constitute the average EP. Salamy[51] and Salamy and Williams[52] have demonstrated that the amplitude depression of late components of the average EP observed after alcohol ingestion primarily represents decreases in single EP amplitudes, rather than increased latency variability.

By recording EPs from various scalp electrode placements in man, it has been observed that alcohol produces a far greater amplitude depression over the association areas than it does over the primary receiving areas. This finding has been reported for both somatosensory[52] and visual[50,56] (and A. Pfefferbaum et al., personal communication, 1977) modalities.

Resistance of the somatosensory cortex to extremely high doses of alcohol (7 g/kg) has been reported in monkeys.[61] Even when the animal was completely nonreactive to its environment, strong EP responses in the somatosensory cortex persisted in response to touching the hand. Interestingly, the posterior parietal association cortex was found to be more sensitive to the effects of alcohol than was the adjacent primary somatosensory cortex. Within the association cortex, however, not all electrode sites are similarly affected by alcohol. Taken together, these results suggest that the various brain regions are differentially susceptible to the effects of alcohol. It has been suggested that the selective sensitivity to alcohol of some brain regions depends on the complexity of its synaptic connections.[62–64] There is a growing literature which indicates that in animals polysynaptic brain sites such as the association cortices and reticular formation are the areas that are most sensitive to alcohol.[5,61,64–68]

Recently, there has been a great deal of interest concerning the lateralized effects of alcohol on cerebral functioning. This interest is an outgrowth of the neuropsychologic findings which indicate that alcoholics tend to perform most poorly on tasks sensitive to right-hemisphere dysfunction or pathology. Specif-

ically, performance on visuospatial tasks has been found to be markedly impaired whereas verbal abilities remain relatively intact in alcoholics given neuropsychologic tests. Normally, visual EPs recorded bilaterally to blank flashes tend to be larger over the right rather than the left hemisphere in healthy subjects at both central[50,57] and occipital sites.[56] These extremely small interhemispheric amplitude asymmetries occur in only some subjects and may be due to measurement as well as methodologic factors such as fluctuations in resistance, amplifier differences, and slight differences in electrode placements at homologous sites. Indeed, a striking degree of interhemispheric symmetry has been reported from homologous bilateral electrode placements in large samples of healthy subjects.[69] Nevertheless, all studies examining the effects of acute doses of alcohol on hemispheric asymmetry indicate that alcohol dissipates preexisting hemispheric asymmetry.[50,56,57]

This dissipation seems to be related to a differential susceptibility of the right hemisphere to the direct depressant effects of alcohol rather than to any preexisting hemispheric electrophysiologic differences. In general, there is a greater reduction of right- as compared to left-hemisphere responses after alcohol intake regardless of whether hemispheric asymmetry was apparent or not prior to the alcohol ingestion.[56] This indicates that more important than the dissipation of asymmetry (which may be spurious) is the finding that alcohol differentially depresses right-hemisphere responses to a greater extent than it does left-hemisphere responses. Perhaps this is due to greater blood flow to the right than to the left hemisphere[70] (and may, therefore, have little to do with cognitive interhemispheric differences).[71] Similar results, indicating a greater alcohol effect on the right hemisphere, have been reported for cerebral blood flow changes in response to alcohol.[72,73] Unfortunately, the effects of alcohol on EPs have not been examined carefully with a left-hemisphere task.

These small interhemispheric differences are rather insignificant in light of the more striking differences in susceptibility when nonhomologous brain loci (e.g., central versus occipital) are compared in response to the effects of alcohol. There is a high degree of symmetry in the various EP components obtained from homologous scalp locations in terms of the magnitude and time course of depression after alcohol administration in comparison to nonhomologous recordings obtained from different scalp regions.[56] Thus, Porjesz and Begleiter[56] have found that bilateral occipital responses recover over a 2-hr period, whereas central responses do not. These studies indicate that the time course for recovery differs between homologous brain regions. The results of this study also suggest that the greater the magnitude of the alcohol-related depression, the slower is the recovery.

It is difficult to determine when, after ingestion of alcohol, its major effect becomes manifest, as dose of alcohol and testing regimens are interactively involved. Low doses of alcohol, those which yield blood alcohol levels (BALs)

of 30 to 65 mg/100 ml, have been found to have little or no effect on visual or somatosensory EPs, whereas high doses, those which yield BALs of 90 to 110 mg/100 ml, greatly depress amplitudes,[50,51,54,59] and the degree of amplitude depression recorded has been found to be related directly to the dose of alcohol administered and the blood alcohol level achieved.[51,52,59]

In a study examining the relationship between BAL and EP amplitude over time,[52] it was found that the N1–P2 amplitude is directly related to the absolute BAL, regardless of whether it is on the rising or falling limb of the BAL curve. However, the relationship between the rate of BAL change and EP amplitude, and whether the same BAL produced by different alcohol doses affects EP amplitude similarly, remains to be elucidated. In our laboratory (unpublished observations), we have found that the N1–P2 amplitude decreases observed after a single alcohol dose are more related to BAL than to time after alcohol ingestion, thus corroborating Salamy's findings.[51,52] However, we observed a great deal of intersubject variability, in terms of both magnitude and time after alcohol ingestion, in which the peak BAL and the maximum EP amplitude reductions occurred. These individual differences may in part be accounted for by differences in food ingested prior to testing and genetic or constitutional differences among subjects.[49,74] Recent evidence suggests that individuals with a family history of alcoholism respond quite differently to alcohol than do individuals without an alcoholism family history.[49] This finding indicates that, in addition to absolute blood alcohol levels, there are other factors that influence the degree of EP amplitude depression and suggests further that a genetic predisposition to alcoholism may contribute to an individual's responsiveness to alcohol.

In summary, there are many factors that can account for the differences in results obtained between individuals and across laboratories. Dose of alcohol administered, testing regimen, stimulus parameters, subject factors (e.g., genetic differences, nutritional status), and control (placebo) groups or conditions are some of the factors that have not been held constant across investigations. Inasmuch as there is substantial intersubject variability with respect to the response to alcohol, the control condition is a critical determinant of the results obtained in a given study. The between-subject variability underlines the importance of using an experimental paradigm that allows each subject to serve as his/her own control in a placebo condition and then be tested in a drug condition.

Cross-sectional designs, although providing valuable information, require inordinately large samples because of the variability of responses between individuals. In the cross-sectional paradigm, the most consistent statistical finding is usually the drug-×-subject interaction effect. Some studies use a predrug baseline as a control condition and then compare EPs before and after alcohol administration. Although determining the predrug baseline is important in an EP experiment, it is not sufficient if it is to be used as the only control condition. The late EP components (N1–P2) are the most sensitive to alcohol in that they

habituate most over time; hence, the N1–P2 amplitude decreases over time regardless of whether or not alcohol has been administered. Thus, although a predrug baseline is a necessary control, the optimal design requires employing a placebo condition at a separate time point in which the subject acts as his own control to determine the specific effects of alcohol.

2.3. Information Processing and ERPs (N1 + P3)

2.3.1. N1–P2

Thus far, we have considered only studies that required normal subjects, under the influence of alcohol, to *passively* attend to stimuli. Attentional factors may interact with alcohol's drug effects to produce the EP amplitude decrements observed. Many brain loci (e.g., association cortex), which are susceptible to alcohol's depressant effects, are also integrally involved in attentional processes. Furthermore, the same EP component (N1–P2) that is significantly depressed by alcohol is the one that is most sensitive to attentional manipulation.

These considerations notwithstanding, attentional factors can be separated from drug effects with the use of ERP techniques. To do so, the subject is required to be engaged actively in specific tasks during the recording of ERPs. The effects of acute doses of alcohol on ERPs recorded during active information processing have been investigated most frequently using visual and auditory target-selection tasks[47–49,57,75,76] (and B. Porjesz and H. Begleiter, unpublished observations). Target-selection tasks require the subject to detect a designated, rarely occurring, target stimulus that is embedded in a series of frequently occurring nontarget stimuli. ERPs recorded to frequently occurring nontarget stimuli elicit N1–P2 components, but not P3, whereas rare target stimuli elicit both N1–P2 and P3 components. Responses to an attended channel (e.g., stimulus modality) elicit large N1 components (a negative deflection approximately 100 msec after the stimulus) when compared to an unattended channel, regardless of whether they are targets or not. The effects of alcohol on P3 will be discussed later in this section.

In studies examining the effects of alcohol on ERPs with the use of target-selection tasks, decrements in the amplitude of N1 to frequently occurring nontarget stimuli over central areas[47,57,76] (and B. Porjesz and H. Begleiter, unpublished observations) but not over occipital areas have been demonstrated.[75] Marked amplitude reductions have been reported at central leads, regardless of attentional factors (e.g., task versus no-task), leading Rhodes and his colleagues[57] to conclude that although both attention and alcohol significantly reduce ERP amplitude, the attention factor exerts less of an effect than does alcohol. Interestingly Obitz et al.[75] were able to counteract alcohol-slowed reaction times, but

not ERPs, with the use of a monetary reward. Thus, despite attentional factors, N1 amplitudes are reduced markedly by alcohol.

Although all target-selection paradigms report N1 decrements from alcohol,[47,57,76] (and B. Porjesz and H. Begleiter, unpublished observations) N1 decrements were not obtained by Roth et al.[77] using a memory retrieval paradigm. These authors[77] postulated that the mobilization of attention under memory-retrieval conditions counterbalanced the alcohol-produced N1 decrements. The discrepancy between the results obtained from the target-selection and memory-retrieval studies can perhaps be explained best on the basis of differences in task requirements and task complexity. It is possible, for example, that attention is mobilized to a greater extent in memory-retrieval tasks than in simple target-selection tasks. Roth et al.[77] did not report any significant reaction time differences between alcohol and placebo conditions, indicating that attention indeed was mobilized in their study.

Although it can be concluded from target-selection studies that the effects of attention on ERP are not as influential as the effects of alcohol[57] and that memory-retrieval studies indicate that alcohol effects are not as strong as attentional effects,[77] these findings may not be as discrepant as they appear at first glance. The net ERP result may reflect an interaction between task and drug effect, possibly as a function of the relative strength of each factor in the particular test situation. It appears, however, that the depressant effects of alcohol can be offset at least somewhat by increased attentional effort that is required in performing a complex task.

2.3.2. *P3*

The P3 or P300 component is a large positive deflection that occurs between 300 and 500 msec after the stimulus. It can only be elicited under certain rather specific conditions where the "subjective significance" of a stimulus involving dimensions of task relevance,[78] unpredictability,[79] or infrequency[80] is a feature of the experimental task, or where certain motivational conditions are present.[81] Elicitation of the P3 component is unrelated to physical stimulus parameters. Indeed, it can be elicited in the absence of an expected stimulus (e.g., emitted potentials). With respect to scalp topography, the P3 component has been found to be maximum over parietal areas. It is bilaterally distributed without apparent hemispheric asymmetry and has a similar distribution for all sensory modalities.[82–84]

The most frequently employed paradigm to elicit a P3 component is the previously described target-selection procedure. ERPs recorded to rare target stimuli elicit large P3 components, whereas frequent nontarget stimuli do not elicit P3 components.

Very few studies have investigated the effects of acute doses of alcohol on

the P3 component. All the target-selection studies investigating P3 components to rarely occurring nontarget stimuli have found significant P3 amplitude reductions after acute alcohol ingestion[47,76] (and B. Porjesz and H. Begleiter, unpublished observations). In fact, Kopell et al.[76] reported that P3 amplitude decreased so rapidly it disappeared in many subjects. Of the studies examining P3 characteristics to task-relevant target stimuli after alcohol ingestion, only Pfefferbaum et al.[47] did not report a P3 amplitude decrement. P3 decrements to target stimuli after alcohol intake have been demonstrated in both visual (B. Porjesz and H. Begleiter, unpublished observations) and auditory[85] target-selection paradigms, as well as in a visual memory-retrieval paradigm.[77]

Elmasian et al.[49] have found that an individual's response to alcohol may be related to a family history of alcohol abuse. They reported that all subjects manifested increased P3 latencies after alcohol ingestion, but only the subjects with family histories of alcoholism additionally manifested decreased P3 amplitudes. P3 latencies have been reported to be delayed significantly after ethanol ingestion to rare target stimuli in auditory target-selection paradigms.[47–49] Slight, but insignificant, P3 latency delays have been reported in auditory[85] and visual (B. Porjesz and G. Begleiter, unpublished observations) target-selection tasks. Although Pfefferbaum et al.[47] observed delays in P3 latencies to rare targets, they did not report P3 delays to rare nontargets. However, Neville et al.[48] emphasize that it is only correctly identified targets that produce P3 delays. These results suggest that processing time may be slower under the influence of alcohol when accurate task-relevant stimulus detection is required.

It is possible that other subject factors (besides family history) remain to be identified to explain the individual differences observed in response to alcohol administration. However, it seems apparent that as with other drugs, individuals do not respond to alcohol in a homogeneous fashion. Nonetheless, the single-dose studies described previously are important because they provide information about the direct effects of alcohol on normal brain functioning. This information is useful for determining the brain loci and the nature of brain functioning that are most susceptible to ethanol's effects and, as such, may provide a clue regarding the brain areas that are affected and the type of dysfunction that is most likely to be manifest after chronic alcohol abuse.[86]

3. CHRONIC ALCOHOL ABUSE

Although a few studies have investigated humans during chronic alcoholization,[87–89] the majority of the studies employing EP measures have been performed on animals. The animal literature indicates that prolonged alcohol administration produces decrements in EP voltages[19] and delays in BSP latencies.[22] These alcohol-related EP changes are attenuated once tolerance develops.[22] The

abrupt removal of alcohol produces a rebound hyperexcitability, characterized by increased EP amplitudes[17,19,23,24,90] and a significant shortening of BSP latencies.[22] This CNS hyperexcitability has been found to persist well beyond the signs and symptoms of withdrawal dissipation (3 weeks).[5,17,19,22–24,91]

The persistence of these electrophysiologic changes has been found to be related directly to the length of alcohol exposure.[23] In one study in our laboratory we found that abstinent animals, challenged with a small dose of alcohol 2 to 5 weeks after withdrawal, manifested increased EP amplitudes (hyperexcitability), whereas naive control animals exhibited depressed EPs to the same dose of alcohol over the visual cortex.[23,24] It should be noted that the EPs were identical in the two groups of animals prior to the challenge dose, indicating that long-lasting CNS changes may at times be so subtle that they can only be detected with the use of a challenge dose of alcohol. Although brain damage and/or dysfunction can be detected with other techniques (e.g., CT scan, neuropsychologic tests), at present only electrophysiologic techniques (e.g., BSPs and EPs) can discriminate between the various concomitants of brain dysfunction associated with alcoholism (intoxication, withdrawal, and long-term subacute brain damage).[17,18] As transient CNS hyperexcitability after alcohol intake can mask or interact with other forms of underlying brain damage, it is difficult to separate CNS dysfunctions that are related to withdrawal from brain deficits caused by repeated chronic alcohol abuse. In order to examine long-term brain damage, it is important to test alcoholics who are abstinent for long periods of time after hyperexcitability has dissipated.

Inasmuch as CNS hyperexcitability has been reported to last as long as 3 weeks, the ensuing discussion is divided into two subsections. First, the studies related to CNS hyperexcitability (<3 weeks postwithdrawal) will be considered. This discussion will be followed by a review of studies investigating long-term brain dysfunction and recovery (>3 weeks). It is emphasized, however, that this dichotomization is somewhat arbitrary and may not be relevant clinically.

3.1. Short-Term Abstinence (Withdrawal)

3.1.1. Auditory BSPs

Chu et al.[22] have reported that BSP latencies in the rat are sensitive indices of acute and chronic alcohol intoxication, alcohol withdrawal, and recovery. These investigators not only replicated their previous finding that acute intoxication results in delaying the central conduction time of peaks III to VII,[20] but also observed delays in peak II. Chronic intoxication for 2 weeks resulted in peak and central conduction time slowing, but to a lesser extent, and only affecting peaks V and VII. This finding suggests that tolerance to alcohol can be reflected in the BSP. The major BSP effect was observed during withdrawal,

when latencies of all peaks and central conduction velocities were shifted significantly earlier than during the prealcohol condition. When half the sample of rats ($n = 5$) were retested during a recovery period lasting up to 8 weeks after alcohol exposure, four of them still displayed shorter peak latencies as long as 3 to 4 weeks postalcohol. By 8 weeks postwithdrawal, all the rats returned to normal peak latencies. Thus, it appears that the underlying concomitants of withdrawal are still apparent long after the acute symptoms of withdrawal have subsided.

3.1.2. *EPs*

For the past several years, we have systematically studied the electrophysiologic concomitants of withdrawal after the cessation of chronic alcohol intake in animals. We have demonstrated that alcohol withdrawal is accompanied by marked increases in EP amplitudes in both rats and monkeys.[5,17,23,24,92] We postulated that these enhanced amplitudes are the result of brain hyperexcitability. The persistence of these electrophysiologic changes was found to be directly related to the duration of alcohol exposure.

Perhaps because of the difficulties involved in conducting this type of research, there is a paucity of studies that have examined human alcoholics during acute withdrawal.[87–89] In one study in our laboratory,[88] we examined recovery of somatosensory EPs in chronic alcoholics during 4 days of intoxication and withdrawal, in which we always began recording 10 hr after the last drink, that is, the "morning after." We found CNS excitability during withdrawal, and that the degree of hyperexcitability was a function of the number of days of prior alcohol intake. Thus, the results of our animal and human studies are in concordance. These findings of rebound hyperexcitability reflected in enhanced EP amplitudes have been replicated recently by others in rats.[19] Increased amplitudes of cortical EPs after alcohol withdrawal have been confirmed also in human alcoholics who have been abstinent for at least 1 week.[89,93–95]

Coger et al.[93] found that alcoholics in "withdrawal" (1 week abstinent) manifest larger visual evoked potential (VEP) amplitudes (P100–N140) than do normal controls. Furthermore, "stabilized alcoholics" (3 to 4 weeks abstinent) exhibit higher VEPs than do controls, but do not differ significantly from the "withdrawal" group. Unfortunately these results were contaminated by drug effects, since all the alcoholics were taking Antabuse (disulfiram), a medication that has been shown to increase EP amplitude.[96] Thus, although it is possible that the increased VEP amplitudes are due to the residual effects of withdrawal and hence persisting CNS hyperexcitability, the findings are not conclusive because of the confounding Antabuse effects. Similar findings have been obtained by Wagman et al.,[89] who examined VEPs in detoxified (7 to 21 days) chronic alcoholics during experimentally induced alcoholization and withdrawal. All the

alcoholics exhibited increased early-component amplitudes (<130 msec) after alcohol removal. This finding was particularly striking in alcoholics who manifested low-amplitude slow-wave sleep (SWS). Overresponsiveness has been demonstrated by Lelord et al.,[94] who reported that alcoholics abstinent from alcohol for 10 days are more responsive to phantom light than are normal controls. The incidence of emitted potentials was higher in alcoholics than it was in controls. Lelord et al.[94] concluded that their findings indicated the presence of CNS hyperexcitability in the alcoholic sample they studied.

Excitability of the CNS has been investigated in chronic alcoholics by measuring the augmenting–reducing information styles. The augmenting–reducing styles were proposed initially by Petrie,[97,98] who measured the kinesthetic aftereffect. Augmenters are individuals who amplify their response to stimulation whereas reducers attenuate their response to stimulation. Petrie observed that most alcoholics are augmenters, and that alcohol ingestion has the effect of lowering the augmentation. Buchsbaum and Pfefferbaum,[99] utilizing an amplitude-intensity gradient (A-I slope), demonstrated that cortical EPs elicited by various light intensities could be used to distinguish between individuals who are augmenters and those who are reducers. Augmenters exhibit increasing VEP amplitude (P100–N140) with increasing stimulus intensity (positive slope), whereas reducers do not demonstrate this relationship (low or negative gradient).[100] Petrie's hypothesis that alcohol ingestion decreases augmentation in augmenters has been confirmed by recording EPs in nonalcoholic augmenters[46,55] (and A. Pfefferbaum et al., personal communication, 1977). Buchsbaum and Ludwig[101] have confirmed Petrie's prediction of decreased augmentation after alcohol administration in alcoholics. Control subjects (reducers) in their study reacted by augmenting their responses after alcohol intake. Buchsbaum and Ludwig[101] concluded that perhaps alcoholics depend on alcohol to inhibit sensory input, as their A-I slope under the highest dose of alcohol most resembled that of sober controls. In fact, alcohol may have a "normalizing" effect on the A-I slope, as has been suggested for many other physiological functions;[102,103] augmenting responses of reducers and reducing responses of augmenters.

The early observation by Petrie that alcoholics tend to be augmenters has been substantiated in several EP studies[93,101,104,105] particularly those in which there has been a family history of affective disorder.[106] This overresponsiveness (hyperexcitability) to high intensities may represent a lack of cortical inhibition in alcoholics. Most of these studies that report enhanced A-I gradients in abstinent alcoholics test their subjects during the first 2 weeks of abstinence when withdrawal symptoms may not have subsided completely. Coger et al.[93] report that alcoholics in "withdrawal" (1 week abstinent) exhibit higher right-hemisphere A-I gradients than controls and "stablized" (3 to 4 weeks abstinent) alcoholics. This finding suggests that as withdrawal diminishes, the A-I slope begins to return to normal. Furthermore, they reported a significant correlation between the mean right-hemisphere VEP amplitude and A-I slope in alcoholics but not

in normal controls. Extrapolating from this relationship, it seems that the higher the VEP amplitude (or hyperexcitability), the greater is the A-I slope, suggesting perhaps a lack of cortical inhibition.

Taken together, these studies indicate that residual withdrawal phenomena (increased EP amplitudes and A-I slopes) persist in the human alcoholic and may last as long as 3 weeks postwithdrawal and possibly even longer. Animal data from our laboratory indicate that the duration of hyperexcitability depends on the length of prior alcoholization. Abstinent animals, challenged with a small dose of alcohol from 2 to 5 weeks after withdrawal, manifest increased EP amplitudes (hyperexcitability), whereas naive control animals exhibit depressed EPs. Animals that were alcoholized for 2 weeks manifest this "latent hyperexcitability" for a shorter time period than do those alcoholized for 4 weeks. In this latter group, enhanced EPs to a challenge dose were exhibited for as long as 5 weeks postwithdrawal. Although the animal investigations suggest that there is a direct relationship between the length of alcoholization and the persistence of observed CNS excitability, it is important to note that this relationship is difficult to assess in the human alcoholic.

Although enhanced cortical EP amplitudes have been reported in abstinent alcoholics as late as 3 weeks postwithdrawal,[89,93–95] the parameters affecting the time course of diminishing hyperexcitability have not been delineated. This is due in part to the fact that alcoholics differ widely with regard to their drinking histories (e.g., pattern, amount, and length of alcohol consumption) and susceptibility to alcohol-related CNS dysfunction (e.g., predisposing factors, tolerance). All these factors influence the strength and duration of the protracted-abstinence syndrome. Furthermore, in many studies the role of medication and length of abstinence on CNS excitability is overlooked. Patients are often tested at widely varying time points within the same study, and only group EP data are reported. Thus, the phase of recovery and level of CNS reactivity (e.g., hyper/hypoexcitability) may be different between alcoholics in the sample, thereby rendering the group data nonrepresentative and relatively meaningless. Although length of abstinence is a crucial variable in determining the extent of the protracted-abstinence syndrome, it is not solely responsible for determining the phase of CNS excitability. As CNS hyperexcitability subsides, it may camouflage more long-lasting forms of brain damage; hence, it is essential that longitudinal studies of unmedicated patients be conducted to separate persisting withdrawal concomitants from the effects of underlying long-term brain dysfunction or damage.

3.2. Long-Term Abstinence

In contrast to the hyperexcitability (decreased latencies of BSPs and increased EP amplitudes) that may be apparent up to 3 weeks postwithdrawal, studies examining electrophysiologic disturbances in alcoholics abstinent for

longer periods of time (>3 weeks) demonstrate CNS hypoexcitability (increased BSP latencies and decreased EP amplitudes). Few studies have systematically examined long-term CNS disturbances and the potential for recovery in medication-free alcoholics. This type of study has been undertaken, however, in our laboratory for BSPs and ERPs[13,95,107–113] and in Beck's laboratory for EPs.[114–116]

3.2.1. *Early Evoked Activity*

We recently recorded auditory BSPs from alcoholics who were abstinent from alcohol for 1 month.[107] We found that they manifest significant delays in latencies and central conduction velocities of peaks II to V. These results are presented in Figure 1 and are remarkably similar to the effects of acute alcohol administration reported by Squires et al. in animals[20] and man.[21] However, the peak delays exhibited by their intoxicated human subjects were not as prolonged as those manifested by the chronic alcoholics in our investigation.[107] Our study provides the first electrophysiologic evidence of brain dysfunction at levels other than neocortex in chronic alcoholics, specifically with regard to increased neural transmission time in the brain stem. The increase in neural transmission time observed may reflect demyelination, which has long been suspected in chronic alcoholics[117] and has been observed in rats exposed to alcohol chronically.[118] It suggests that long-term alcohol abuse results in demyelination of auditory pathways beginning at the level of pontine formation. Similar results have been reported recently in neurologically impared abstinent alcoholics.[119–121]

In an extensive study of 66 chronic alcoholics, Chu et al.[121] reported that the alcoholics with cerebellar degeneration had the highest incidence (83%) of abnormal BSPs. Furthermore, they found a high correlation between CT scan cerebral atrophy and BSP delay. The greater the number of neurologic complications, the greater was the likelihood of BSP aberration, regardless of the type of neurologic complication. These results suggested to the investigators that the neuropathologic processes underlying cerebral atrophy are diffuse, and perhaps include brain stem involvement.

Increases in BSP latencies were not reported in rats after 2 weeks of chronic alcohol administration.[22] During the early abstinence phase (acute withdrawal) the BSPs were observed to occur earlier than they did prior to alcohol ingestion. The "recovery" was characterized by progressive increases of peak latencies that eventually returned to the prealcohol baseline levels. Perhaps it is only with repeated and prolonged exposure to alcohol that more severe increases in central transmission time (suggesting demyelination) occur. In our study, the alcoholic patients studied had been drinking a minimum of 6 years and for an average of 16 years. Nutritional deficits are known to lead to demyelinating diseases such as polyneuropathy.[122] Thus, it is possible that nutritional deficiencies in and of themselves may have been responsible for demyelination and hence the BSP delays observed.

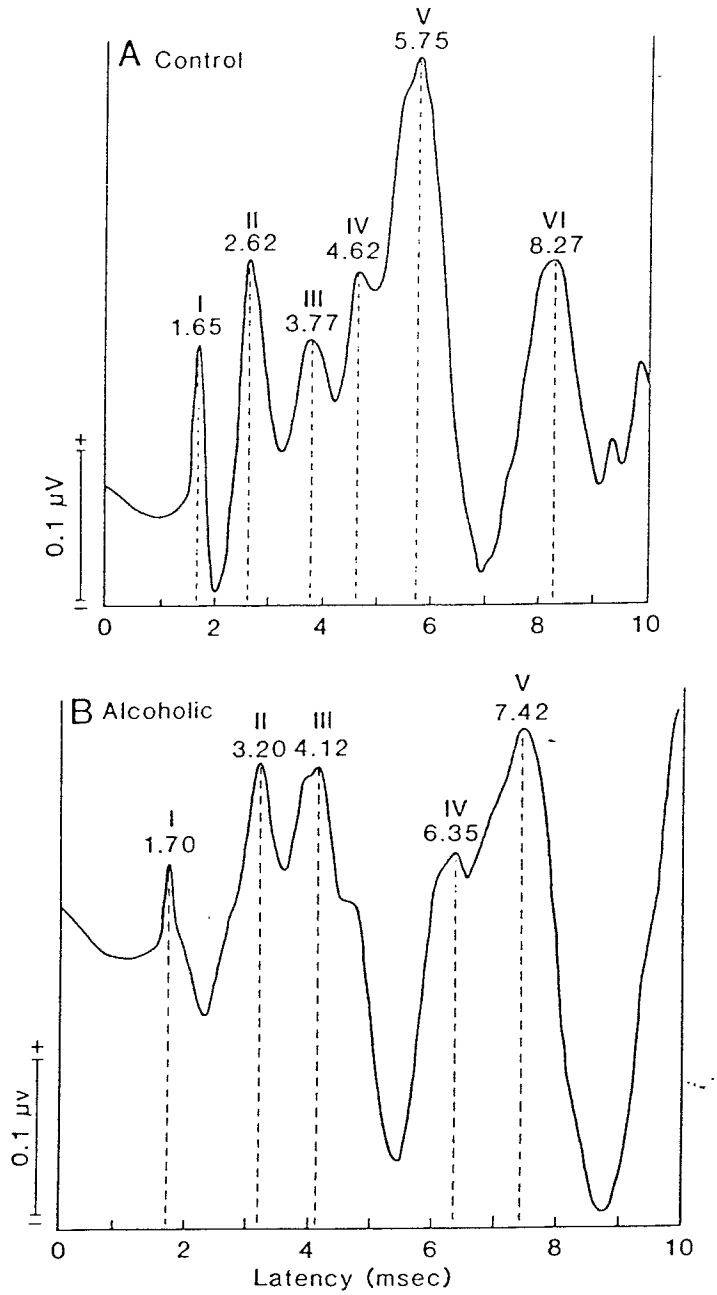

FIGURE 1. (A) Auditory brainstem potential (BSP) for one control subject indicating the latencies of peaks I to VI. (B) Auditory brainstem potential (BSP) for one alcoholic subject, with the latencies of peaks I to V indicated. Notice the delays in peaks II to V in the alcoholic subject when compared to the control subject. Wave VI is delayed beyond 10 msec and therefore is not shown.

The drinking history factor(s) or interaction of factors (e.g., length of drinking history, amount consumed per occasion, number of withdrawals, nutritional factors) that result in brain stem aberrations has not yet been determined. At present we are investigating the relationship between these and the magnitude of the recorded BSP aberrations. Our preliminary data suggest that alcoholics with signs of nutritional deficiency and/or polyneuropathy display different BSP wave forms than do alcoholics without these signs. Furthermore, length of drinking history does not seem to correlate with BSP delay; in fact, alcoholics with relatively short but heavy drinking histories (<8 years) who have evidence of nutritional deficiency manifest greater BSP aberrations than do alcoholics with long drinking histories (>20 years) and no signs of nutritional disturbance.

Taken together, the preliminary findings suggest that BSP aberrations in chronic alcoholics may be the result of alcohol and/or nutritional factors. The results of animal studies[22] suggest that some factors in addition to chronic exposure are necessary to produce the BSP abnormalities, as chronic alcohol ingestion by itself does not result in BSP delays after withdrawal. At this point, the relationship between early EP measures, nutritional status, and drinking history remains to be determined.

3.2.2. *Late Evoked Activity (ERPs)*

Few studies in chronic alcoholics have been conducted in which EP or ERP techniques have been utilized to investigate long-term (>3 weeks) brain dysfunction. Over the last decade, Beck and his colleagues[114–116,123] have recorded VEPs in abstinent (<93 days) chronic alcoholics who passively attended to repetitive flashes. Late-component amplitudes (N1–P2), but not early-component amplitudes (P1–N1), were found to be depressed.

More recently, investigators have applied ERP techniques in which the subject is actively engaged in a task. Target-selection paradigms have been used for recording ERPs in the auditory[47,124,125] and visual[13,108–113] modalities, as well as both together (bimodal).[95,126] In most of these investigations a decrease in late-component amplitudes (N1–P2 and P3) and delayed late-component latencies (hypoexcitability) have been found. Although all the studies concur that it is the late components (N1–P2 and P3) that are most aberrant in chronic alcoholics, it should be noted that differences in results have been reported between the various laboratories. These discrepancies probably can be attributed to (1) differences in the characteristics of the patient samples tested (e.g., presence of neuropsychologic deficits, genetic factors, age, sex); (2) differences between samples in the subjects' drinking histories (length and pattern of alcohol consumption, length of abstinence); and (3) methodologic variations (e.g., passive attention versus active involvement, speed versus accuracy strategies, task complexity, stimulus modality, electrode type and placement, ERP measurement procedures).

Although most studies concur that the N1–P2 amplitude recorded over the association cortex is diminished in long-term abstinent alcoholics, this finding is not obtained if the subjects have been taking Antabuse (disulfiram).[93,115,125] Interestingly, Peeke et al.[96] have reported increases in ERPs in healthy volunteers administered disulfiram. Such contamination of results due to medication is particularly critical when "recovery" of brain dysfunction is being investigated.[93,125]

For the past several years, we have systematically examined ERPs in medication-free abstinent chronic alcoholics. The ERP techniques employed require the subject to engage in some information-processing task. Each task is designed to examine disturbances of a particular ERP component which has been well documented in the electrophysiology literature to vary in a predicted way under certain conditions in normal subjects. 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.[95] The N1 component is sensitive to the selection of either a relevant or irrelevant stimulus modality. In healthy subjects, the N1 component is enhanced to all stimuli in a relevant stimulus modality and decreased to stimuli in all irrelevant modalities.[127–129] A sequence of randomized flashes and clicks were presented to the patient. Interspersed among frequently occurring single flashes and clicks were rarely occurring double flashes and double clicks. The patient was required to "shift attentional sets" by counting either the double flashes or the double clicks, or ignoring all stimuli in an otherwise identical stimulus sequence. ERPs were obtained only to the irrelevant single flashes, which were in either the relevant or irrelevant stimulus modality in a given condition. These frequent single flashes elicit N1 but not P3 components that are enhanced differentially in the relevant channel or stimulus modality. The results of this investigation indicate that abstinent alcoholics manifest abnormally reduced late-component (N1–P2), but not early-component, amplitudes, particularly over right-hemisphere frontal and central scalp loci. Furthermore, less hemispheric asymmetry (right-hemisphere amplitudes larger than left) was evident in the alcoholics than in the controls. These findings with abstinent chronic alcoholics are remarkably similar to the results in which acute doses of alcohol were administered to healthy individuals,[54,56,57] suggesting the possibility that the electrophysiologic brain dysfunction observed in sober chronic alcoholics resembles the brain functioning of normal persons who are under the influence of alcohol.

Our ERP results, obtained while the alcoholic patient was actively engaged in a task, confirm previous findings in which alcoholics passively attend to repetitive flashes.[114,115] The advantage of using an information-processing ERP design to assess brain functioning is that it is not possible with passive EP techniques to compare responses to identical relevant and irrelevant inputs. Often it is the differential voltage between relevant and irrelevant stimuli that is more

revealing about the nature of brain function than the absolute voltage to either stimulus. Consistent with the ERP literature,[127,128] control subjects in our study[95] demonstrated enhanced N1 components to stimuli in the relevant as opposed to the irrelevant modality. In contrast, alcoholics maintained the same low amplitude for N1 regardless of the condition of task relevance. This finding suggests that chronic alcoholics may be incapable of appropriate "sensory filtering" as they do not differentiate between relevant and irrelevant channels.

In another study, we investigated brain dysfunction in chronic alcoholics by measuring the P3 component in a target-selection visual ERP paradigm.[109] We were interested in the ability of alcoholics to differentiate between relevant and irrelevant events, and in their ability to probability-match stimuli according to their frequency of occurrence. The stimuli were geometric shapes that differed in their frequency of occurrence. One rarely presented geometric shape (e.g., triangle) was designated the target. The subject was required to press a button in response to that stimulus only. Target and nontarget stimuli were alternated on every other block of trials, thereby enabling the recording of ERPs to the same stimulus when it was the target, and when it was the 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). Because the stimuli were all in the relevant modality, they would be expected to elicit large N1 amplitudes. Only the rare stimuli would be expected, however, to elicit the P3 component in this experimental design.

As in our bimodal experiment,[95] we found that the late-component amplitude (N1–P2) was depressed in alcoholics to all stimuli (target, nontarget, and novel) to levels comparable to an irrelevant stimulus modality, suggesting that "sensory-filtering" mechanisms were impaired.

Furthermore, we found that P3 amplitudes were depressed or absent in alcoholic patients to rare target stimuli under conditions optimal for eliciting large P3s.[79] This finding was most striking over the parietal areas, where P3 amplitude is maximal.[83,84,130] A comparison of the ERP to the target stimulus in the control group (Figure 2) and the ERP to the target stimulus in the alcoholic group (Figure 3) illustrates this voltage reduction in the alcoholics. Furthermore, although normal controls manifest differentially enhanced late P3 components to target stimuli (Figure 2), alcoholics manifest identical low-amplitude P3 waves with the same P3 latencies regardless of whether a stimulus was a target or nontarget (Figure 3). Thus, the major aberrations manifested by chronic alcoholics were a lack of differentiation between ERP responses to relevant and irrelevant inputs and low event-related voltages. This seems to suggest underlying brain dysfunction which impairs sensory-filtering and probability-matching processes.

It has been suggested that the P3 or P300 component of the ERP is a

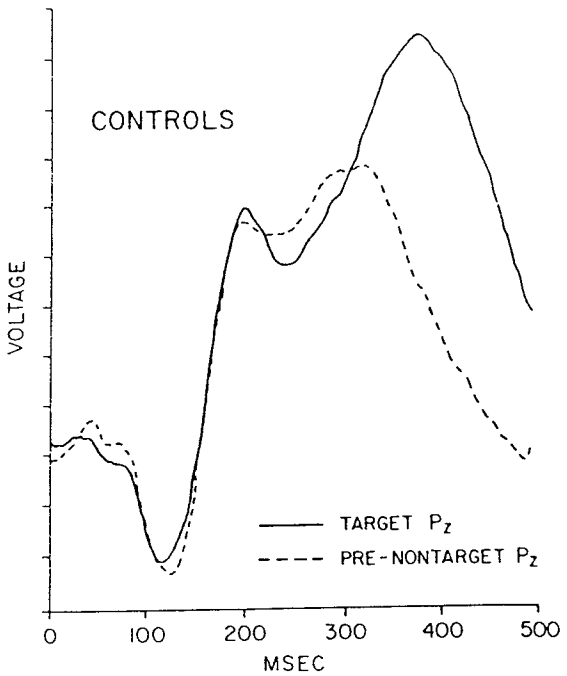

FIGURE 2. Grand mean ERP wave forms recorded at parietal electrode (P_z) to the target stimulus (solid line) and nontarget stimulus (dashed line) in healthy subjects. Notice the prominent P_3 component (large positive deflection occurring between 300 and 450 msec) to the target stimulus.

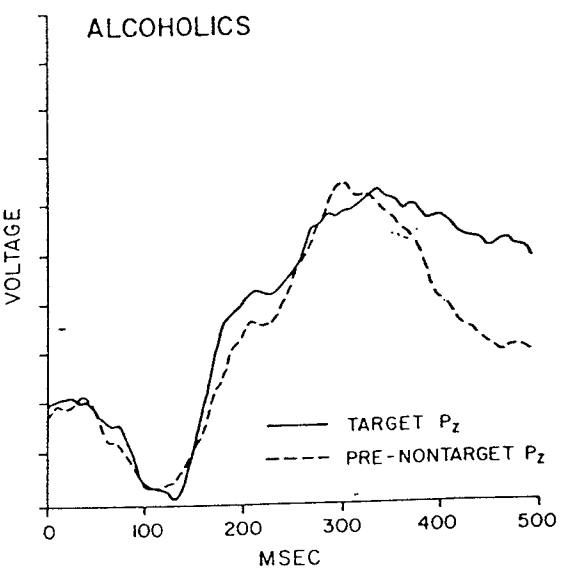

FIGURE 3. Grand mean ERP wave forms recorded at parietal (P_z) to the target (solid line) and nontarget (dashed line) stimuli in the alcoholic group. Compare the P_3 component of the target stimulus to that of the control group (Figure 2), and notice how reduced it is in amplitude. Also notice the lack of difference between P_3 amplitudes to target and nontarget stimuli in the alcoholic group in this figure.

manifestation of the orienting response.[130-133] Certain non-modality-specific hippocampal neurons are reported to be involved in this response.[134] These non-modality-specific neurons "compare" incoming stimuli and react to significant or novel stimuli while inhibiting responses to repeated stimuli. Despite its maximal amplitude over parietal areas at the scalp, evidence suggests that the neural origins of P300 may be subcortical, and in particular they may arise from the amygdala and hippocampus. Thus a recent study investigating the neural origin of P3 with implanted electrodes in humans reported that the P300 was maximum at these subcortical loci.[135] This finding was confirmed by Halgren et al.,[136] who recorded large late potentials from the limbic system in humans with implanted electrodes and postulated that the P3 may be generated in the hippocampus or amygdala.

Thus, our results, demonstrating that chronic alcoholics manifest low-voltage or even absent P300 components under conditions designed to elicit maximum P3 component amplitudes, may indicate a hippocampal deficit. Although the contributions of cortical sites cannot be ruled out, the results obtained underscore the important role of limbic structures in generating the P300 component. The involvement of the hippocampus in chronic alcohol intake in the absence of malnutrition has been demonstrated in neuropathologic[7,137,138] and neurophysiologic[5,7,137,138] studies in animals. Long-term ethanol consumption has been found to result in the attrition of dendritic spines in mouse[137] and rat[138] hippocampus. Relevant to this issue we have demonstrated a susceptibility to both acute and chronic alcohol effects on EPs recorded from the monkey hippocampus.

We have become interested in determining the relationship between electrophysiologic deficits and widened cortical sulci observed in chronic alcoholics.[13] Two groups of alcoholics who had received CT scans after 1 month of abstinence were selected for the study. The first group manifested a high degree of widened cortical sulci (Pos-CT), whereas the second group did not have evidence of cortical atrophy (Neg-CT). Patients in the two groups did not differ with respect to age, education, or drinking history (duration and amount). ERPs were recorded the same day the CT scans were obtained and involved the same P3 paradigm described previously.[109] Alcoholics with enlarged cortical sulci (Pos-CT) had a lower (or absent) P300 amplitude to target stimuli than did the alcoholics without such enlarged cortical sulci (Neg-CT). This finding suggests that cortical changes (shrinkage or perhaps even atrophy) may play a role in determining the P3 amplitude depression in alcoholics. However, as shown in Figure 4, both groups of alcoholics (Pos-CT and Neg-CT) manifested lower P3 amplitudes to target stimuli than did the normal controls. Furthermore, both groups of alcoholics displayed similar P3 components to all categories of stimuli, regardless of task relevance. These findings replicate previous results in chronic alcoholics who were not classified on the basis of their CT scan characteristics.

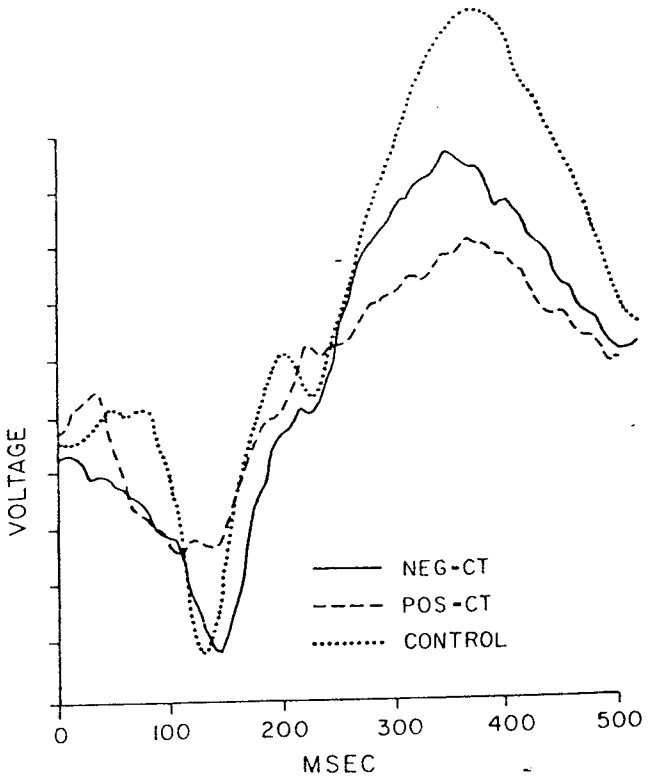

FIGURE 4. Grand mean ERP wave forms recorded at parietal electrode (P_z) to a visual target stimulus in control subjects (dotted line), alcoholics with negative CT scan (solid line), and alcoholics with positive CT scan (dashed line). Notice that the amplitude of the large positive deflection occurring between 300 and 400 msec (P_3 component) is smaller in the group of alcoholics with a positive CT scan than in those with a negative CT scan. However, notice that the amplitude in both alcoholic groups is smaller than in the control group.

Inasmuch as alcoholics without widened cortical sulci manifest diminished P300 amplitudes when compared to healthy nonalcoholics, it can be concluded that neocortical shrinkage alone cannot explain these changes. The findings suggest that in man, chronic alcohol abuse results not only in changes within the neocortex but also in electrophysiologic aberrations that indicate other brain (e.g., hippocampal) deficits. Often the neocortical deficits are emphasized but subcortical aberrations are overlooked. Our results suggest that alcoholics who have widened cortical sulci are more likely to manifest hippocampal deficits, supporting the hypothesis that chronic alcohol abuse produces diffuse brain damage.

Recently we have completed a study examining the N2 or N200 component of the ERP in abstinent alcoholics.[111,112] The N2 component is a modality-specific negative deflection with a maximum amplitude over the occipitoparietal scalp for the visual modality and over central regions for the auditory modality. Evi-

dence suggests that the latency of N2 can be taken as an index of stimulus evaluation time,[139] as it increases for more difficult discriminations.[140–142] In fact, the N2 component may be a better index of stimulus evaluation time than is the behavioral measure of reaction time (RT). RT is a complex measure of the cumulative time required for stimulus evaluation, response selection and organization, and finally the overt motor response. Therefore, although there are reports of delayed RTs in alcoholics,[143–145] these studies cannot determine which aspect(s) of the information-processing function are impaired. We were interested in examining the speed of stimulus evaluation in alcoholics employing as the index of measurement the N2 component of the ERP. To accomplish this, we designed an RT study involving easy and difficult line orientation discriminations. This visuospatial task enabled us to investigate the relationship between difficulty of discrimination, N2 latency, P3 characteristics, and RT in abstinent alcoholics. ERPs were obtained to frequent nontargets (vertical line) and infrequent easy (90° deviant from vertical) and difficult (3° deviant) line orientations.

Our results indicate that the N2 latency reflects difficulty of discrimination in the control subjects, being delayed significantly in the difficult as compared to the easy discrimination condition. These results are presented in Figure 5. However, in the alcoholics there were few differences in N2 latency associated with increasing difficulty of discrimination. Furthermore, the N2 latency occurred significantly later in the alcoholic group than it did in the control group for both easy and difficult discriminations (see Figure 5). This suggests that alcoholics find the discrimination task more difficult and hence require more time for stimulus evaluation. The latency difference between groups was even more apparent for the easy discrimination than it was for the difficult discrimination. This finding suggests that alcoholics need proportionally more time than do controls to make an easy (vertical from horizontal) as compared to a difficult discrimination. In addition, alcoholics manifest delayed P3 latencies to easy discriminations; when compared to controls, their P3 latencies are comparable to those expected for a difficult task. These results suggest that alcoholics adopt a mode of responding that is undifferentiated and independent of task requirements. Essentially, they find all tasks difficult. Thus, although the N2 amplitude was larger for easy discriminations than difficult discriminations in the control group, the N2 amplitudes were the same in the alcoholics regardless of task difficulty. In normal subjects the amplitude of N2 has been shown to be directly related to degree of stimulus deviance.[146] There were no significant differences in RTs between the two groups of subjects, although the alcoholics tended to have somewhat faster RTs than did the controls. However, alcoholics tend to make more errors, in terms of both false alarms and missing target stimuli, suggesting that alcoholics employ different response strategies than do controls and that they stress speed over accuracy of performance.[147] This finding perhaps reflects a lack of inhibition in chronic alcoholics.

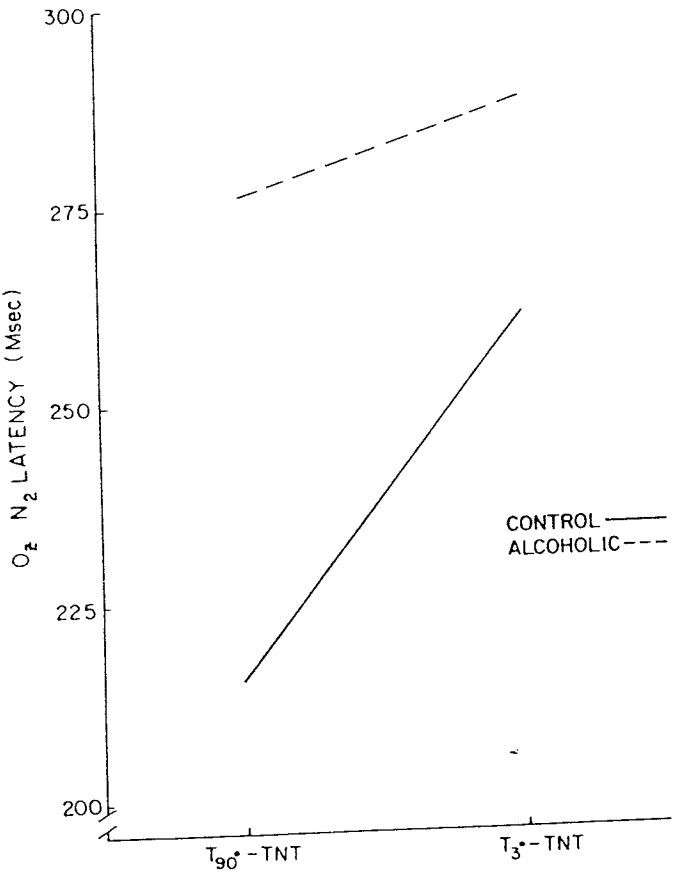

FIGURE 5. Mean N_2 latencies in control (solid line) and alcoholic (dashed line) groups based on subtraction wave forms (T–TNT) for easy ($T_{90°}$–TNT) and difficult ($T_{3°}$–TNT) discriminations. Notice that the latency of N_2 increases significantly with task difficulty in the control group ($P < 0.001$) but not the alcoholic group. Also note that N_2 is significantly later in the alcoholic group than the control group for both the easy discrimination (61 msec, $P < 0.001$) and difficult discrimination (28 msec, $P < 0.05$).

In addition to the latency results, we confirmed our previous findings that alcoholics have depressed P3 amplitudes.[13,109,110,113] This low amplitude was most apparent for the easy discrimination on which the controls exhibited very high voltages. The P3 voltage was significantly higher for the 90° target when compared to that produced by the 3° target in the control but not in the alcoholic group. This result was predicted by ERP studies which demonstrate that the more deviant a rare stimulus is from its background, the larger is the resultant P3 amplitude.[141,148-151] Perhaps this lack of P3 amplitude difference in the alcoholic group indicates that they are more uncertain of the correctness of their decision than are the controls. This is suggested further by the fact that in the RT paradigm they stress speed over accuracy. Furthermore, whereas controls

manifest significantly different P3 measures to target/nontarget, alcoholics do not. Thus, on the basis of both the N2 and the P3 ERP components, it can be concluded that alcoholics have difficulty evaluating the potential significance of a stimulus. They do not differentiate electrophysiologically between relevant and irrelevant stimuli, or easy and difficult discriminations, but rather maintain the same ERP characteristics regardless of the task requirements. These results indicate that the template for making match/mismatch decisions either is lost or is not readily available to alcoholics. In either case, the findings implicate a memory deficit such that each incoming stimulus must be evaluated anew. The data suggest that alcoholics manifest two types of brain dysfunction; that is, a delay in N2 latency, which suggests that the template for comparison is not readily accessible, and a low P3 voltage, which suggests that once retrieved, the match/mismatch processes are themselves impaired.

Despite the consistency of our results obtained across studies with regard to N1 and P3 amplitude decrements in chronic alcoholics, they are at variance with the results reported by Pfefferbaum et al.,[47,124] who used an auditory RT target-selection task. In contrast to our findings, no N1–P2 or P3 amplitude differences between alcoholics and controls were observed for any stimuli (rare targets and nontargets and frequent nontargets) in their studies. P3 latencies were delayed to all rare stimuli, whether target or nontarget, whereas the latencies of N1 and P2 were not different between the groups. Behaviorally, the alcoholics and controls did not differ from each other with respect to either reaction time or the number and type of errors committed in the task.

Pfefferbaum et al.,[47,124] noting that the ERP pattern of delayed P3 without delays in latencies of N1 and P2 is similar to that reported for dementias[152] of different etiologies, concluded that ERPs of chronic alcoholics resemble those of demented patients. However, Goodin et al.[152] demonstrated this ERP pattern for all demented patients, regardless of etiology of the dementia. Patients with the same medical diagnosis (e.g., hydrocephalus, cerebrovascular disease, or even alcoholism) not displaying evidence of dementia do not exhibit this ERP pattern. Significantly, the alcoholic sample Pfefferbaum et al.[47] examined were clearly not demented; in fact, on the Halstead–Reitan neuropsychologic test battery, only three of ten had scores that were below normal. Furthermore, only the demented patients in the study of Goodin et al.[152] showed latency shifts and a decrease in P3 amplitude. Pfefferbaum et al.[47] did not observe P3 amplitude decrements in their chronic alcoholics, and in fact reported a slight, although nonsignificant, P3 amplitude increase. Therefore, the ERP pattern observed in chronic alcoholics by Pfefferbaum et al.[47] is quite different from that reported for dementia by Goodin et al.[152]

The ERP findings of Pfefferbaum et al.[47] reported for chronic alcoholics also differ from those reported in other laboratories where decreases in N1–P2 amplitudes and delayed latencies have been observed for both auditory[125] and

visual[95,109,114–116,125] stimuli. Less data are available about P3 deficits in chronic alcoholics. Although the experimental design of Salamy et al.[125] is a P3 paradigm, inexplicably they only discuss their N1–P2 results in chronic alcoholics. Thus, the only two laboratories reporting P3 aberrations in chronic alcoholics report discrepant results. We recently confirmed our findings of P3 amplitude decrements in chronic alcoholics under various different experimental paradigms.[111,112,126,153]

Many factors may account for the reported discrepancies of which the most important is the difference in the alcoholic patient populations investigated by the two laboratories. Significantly, the patient populations are entirely different in terms of socioeconomic status, social intactness, age, neuropsychologic status, and length of abstinence from alcohol.

In terms of neuropsychologic function, our patients seem to be more deteriorated than those of Pfefferbaum et al.[47] For example, about 60% of our patients were impaired on the digit symbol test, and at least 40% were impaired on the trailmaking, symbol–digit, and Benton visual retention tests.[154] In contrast, most patients in the Pfefferbaum et al.[47] sample scored within the normal ranges on the Halstead–Reitan neuropsychologic battery (A. Pfefferbaum, personal communication, 1981). Furthermore, our subjects tended to be unemployed and to be recurrent alcoholics with either an unstable or nonexistent family life, whereas the subjects of Pfefferbaum et al.[47] were socially intact.

It is possible that genetic factors may account for these discrepant results. A very high percentage of the alcoholics in our sample (67%) had family histories of alcoholism, whereas those of Pfefferbaum may not have had a genetic predisposition. The subjects' ages were another difference between the alcoholic sample studied by Pfefferbaum et al.[47] and ours.[109] Recently, we have demonstrated that boys whose fathers are alcoholic are more likely to manifest low P3 voltages than are control boys.[157] This issue will be discussed later in Section 4, "Predisposing Factors." The group of alcoholics investigated by Porjesz et al.[109] had a mean age of 36, whereas those examined by Pfefferbaum et al.[47] had a mean age of 50.1. As the ERP is very sensitive to the effects of aging,[110,113,149,155,156] this latter variable may have interacted with the alcohol effects. In addition, length of abstinence, which has been demonstrated to affect the ERP,[93,125,158,159] may contribute to the difference in results observed between the two laboratories. Although Pfefferbaum's patients were abstinent for a minimum of 3 weeks, our subjects were abstinent for an average of 2 months.[13,108–110,113] However, in more recent studies, we have replicated our previous P3 findings in alcoholics who were abstinent from 26 to 30 days (<1 month) and for as long as 4 months.

In addition to differences in patient populations, there are differences in measurement techniques and experimental designs. With respect to measurement of the ERP, Pfefferbaum et al.[47] used Woody filtering to correct latency jitter

in the ERP. We currently are employing similar procedures [latency-corrected averages (LCA)] to determine whether our P3 amplitude results will change with the use of this technique. Recent data using LCAs indicate that the P3 amplitude reduction exhibited by alcoholics is due predominantly to decreased voltages on single trials and is not due to latency variability.[153] Other discrepancies in experimental design may account for the differences in results reported between the two laboratories. Pfefferbaum et al.[47] stressed speed of responding by using an RT task. In contrast, speed was not a factor in our study. It has long been known that P3 characteristics differ depending on whether speed or accuracy is emphasized.[147] It should be noted that we recently used an RT task and did in fact obtain P3 latency delays (in addition to amplitude reductions) in abstinent alcoholics, but only to easy and not difficult discriminations.[112] This finding suggests that task difficulty and speed-versus-accuracy strategies indeed may have contributed to the differences between our visual target-selection paradigm using geometric shapes[13,109,110] and the auditory tone discrimination target selection procedure reported by Pfefferbaum et al.[47]

Thus, the differences in results between our laboratory and that of Pfefferbaum may not be as discrepant as they first appear. Although the latency results can be explained on the basis of certain experimental variables, the amplitude differences may be due to substantial inherent differences in the patient populations studied. The problem of identifying brain dysfunction in alcoholics on the basis of ERP measures seems more complex than had heretofore been thought. Indeed, the components themselves are more complicated and versatile in terms of detecting underlying functional brain deficits than had been assumed previously. ERP components are extremely sensitive to rather specific and often subtle factors, but respond reliably and predictably in healthy individuals, once the critical underlying variables are identified and delineated. Therefore, once the origins and functional utility of each of these components are elucidated definitively, the ERP complexity will prove to be an advantage rather than a drawback in delineating specific aspects of brain functioning in chronic alcoholics.

3.3. Reversibility

The issue of reversibility of brain electrophysiologic aberrations in abstinent alcoholics has not received a great deal of attention. At present, it is difficult to assess the few studies that have attempted to address this issue because in actuality "detoxified" rather than "recovered" alcoholics were tested. Inasmuch as the various electrophysiologic measures are particularly sensitive to withdrawal phenomena and the associated electrophysiologic changes persist for a long period of time, far outlasting overt withdrawal symptomatology,[23,24] the reported "reversibility" may in reality be a reflection of subsiding withdrawal concomitants. In addition to the problem of residual withdrawal symptomatology masking other

forms of underlying brain damage, there is the problem of medication effects. The only two evoked potential investigations comparing alcoholics at different time points after withdrawal[93,125] studied subjects who were taking Antabuse (disulfiram). Coger et al.[93] reported higher ERP amplitudes in patients receiving disulfiram as compared to other patients. In light of the findings of Peeke et al.[96] that ERPs are increased in healthy volunteers who are experimentally administered disulfiram, it can be concluded that "reversibility" cannot be assessed in persons who are receiving this medication for their alcoholism.

Despite the similarities in postwithdrawal testing periods, the results obtained in the two studies are quite different. Coger et al.[93] found that at both 1 week and 3 to 4 weeks postwithdrawal, alcoholics manifest higher amplitudes than do controls. Within the alcoholic group studied, there were no differences between the amplitudes recorded at 1 week and 3 to 4 weeks postwithdrawal. It should be noted, however, that Coger et al.[93] employed a cross-sectional study in which different subjects in the 1-week and 3-to-4-week groups were tested.

In direct contrast to these findings, Salamy et al.[125] reported that N1–P2 amplitudes, recorded during auditory, target-selection tasks, were significantly lower at 1 week at all recording leads (F3, F4, P3, P4). After 3 additional weeks of abstinence, the amplitudes were found to recover over the parietal, but not over the frontal leads. Unfortunately, during the first week of abstinence, prior to testing, patients were administered Librium (chlordiazepoxide) for 4 days and thereafter were receiving Antabuse (disulfiram). By the time of retesting, the subjects had been taking disulfiram for over 3 weeks. Thus, at the time of the first test, the subjects had just changed medications; hence the interactive effects of detoxification from alcohol, chlordiazepoxide, and disulfiram could have contributed to the apparent recovery phenomena. This is the same methodologic problem that was discussed previously with respect to the data reported by Cannon[115] and Coger et al.[93] In each of these studies, low-voltage late component amplitudes were not observed while the patients were on a long-term regimen of disulfiram. From these results, it is difficult to ascertain whether the changes in amplitude were due to the effects of subsiding withdrawal, disulfiram, an interaction between detoxification and medication, or recovery from brain damage.

We are currently examining BSPs and ERPs after 3 weeks and 3 to 4 months of continued abstinence in hospitalized alcoholics. The preliminary BSP findings after almost 4 months of abstinence in one alcoholic are presented in Figure 6 and indicate improved wave form morphology, reduction of latencies, and improved conduction times. The group data demonstrate, however, that the wave form peaks are still occurring somewhat later in the alcoholics than in the controls.

The relative contribution of alcohol abstinence and nutritional factors on so-called "recovery" remains to be determined. Throughout the long-term abstinence program, patients in our study were frequently receiving vitamin therapy

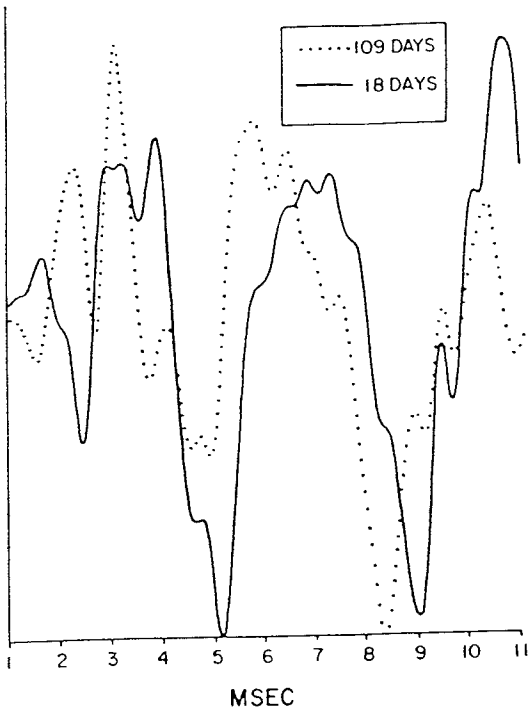

FIGURE 6. Auditory brainstem potential (BSP) in a chronic alcoholic after 18 days (solid line) and 109 days (dashed line) of abstinence. Notice that the latency of the major large complex (waves IV to V) occurs earlier after prolonged abstinence.

and thus may have been manifesting improvements in nutritional status concurrent to abstinence. Furthermore, the role of alcohol withdrawal cannot be overlooked. Nervous system hyperexcitability may be followed by a period of subacute hypoexcitability. It is conjectured that one manifestation of this hypoexcitability is a prolongation of brain stem latencies due to edema. It should be noted in this regard that edema resulting from osmotic stress can lead to demyelination.

Moreover, alcoholics who remained in treatment for the full 4 months had less impaired BSPs at initial testing. It is, therefore, possible that the sample in which reversibility was assessed at 4 months was less impaired in the first place and therefore may not have been representative of the alcoholic population in general. Indeed, our neuropsychologic data indicate that this may be the case.[154] Patients remaining in long-term treatment tend to be less impaired in most neuropsychologic tests administered at initial testing. We are currently in the process of determining whether there is any relationship between neuropsychologic test scores and EP measures.[160] It is still not clear, however, whether more improvement is demonstrated by the alcoholics who are less impaired. Since we are able to examine reversibility only in alcoholics who remain in long-term treatment, and it is these alcoholics who tend to be less impaired initially, it is not known whether recovery occurs in all alcoholics regardless of the severity of initial impairment. It also remains to be determined whether recovery occurs

as a function of the degree of initial impairment, that is, whether greater initial impairment requires a longer time period 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. We examined the possibility of reversibility of late-component P3 deficits in abstinent alcoholics after 3 weeks and 4 months of abstinence. Interestingly, no reversibility in ERP morphology or late component amplitude was noted after 4 months of abstinence in the alcoholics; in fact, the wave forms were strikingly similar at initial and retest time points. Furthermore, there was no improvement in the differential enhancement of P3 amplitudes on the basis of task relevance to target stimuli. Thus, even after 4 months of abstinence, abnormally low P3 amplitudes are still manifest. Moreover, the P3 response decrements have been observed for both auditory and visual target stimuli after 3 weeks and 4 months of abstinence in a bimodal target-selection paradigm. Overall, these results suggest that the P3 deficits may not be reversible, or perhaps reverse more slowly.

In another investigation, we have examined electrophysiologic aberrations in a group of nonhospitalized alcoholics who have been sober from 3 to 10 years. In this sample, normal BSPs were observed. This finding suggests that 4 months is too short a time span to determine whether reversibility of brain dysfunction can take place after many years of heavy drinking. However, it should be noted that the long-term-abstinent alcoholics (>3 years) were not tested at the initial stage of withdrawal. Therefore, the extent of BSP aberration that they may have manifested immediately after alcohol abuse is not known. The possibility that these alcoholics may never have exhibited BSP delays cannot be ruled out. Although the issue of reversibility is still unresolved, the available data point to slow recovery from BSP deficits after prolonged abstinence. However, since no recovery of P3 deficits was observed after a prolonged sobriety period (>3 years), the data suggest that no recovery of P3 deficits occurs after long-term abstinence. Thus, it appears that certain electrophysiologic aberrations observed in chronic alcoholics improve (e.g., BSP), whereas other electrophysiologic aberrations do not change (e.g., P3). In interpreting these results, it is necessary to exercise caution, since the findings obtained to date are based on relatively small samples.

4. PREDISPOSING FACTORS

It has generally been assumed that brain abnormalities observed in alcoholics are due to the toxic effects of alcohol on the brain, nutritional deficits, or the interaction between alcohol and nutritional-related factors. Despite many years of research in this area, the etiology of brain dysfunction in alcoholics remains

unclear. For example, duration of drinking history has not been found to be closely related to CT scan or neuropsychologic or electrophysiologic deficits found in alcoholics. Similar drinking histories often result in different manifestations of brain dysfunction; indeed, some individuals appear to be very resistant whereas others seem to be very susceptible to alcohol's deleterious effects.

The possibility that certain of the brain deficits observed in alcoholics precede alcohol abuse was suggested only recently. This question is raised in conjunction with evidence that certain individuals are at high risk for developing alcoholism.

Sons of alcoholic fathers are approximately four times more likely to develop alcoholism than are sons of nonalcoholics.[161,162] Studies of male adoptees indicate that the biologic father rather than the adoptive parent is predictive of a drinking problem in the proband.[162-167] Studies of twins indicate that the concordance rate for alcohol abuse among identical twins is almost double the rate for fraternal twins.[168] Patterns of alcohol consumption have been found to be highly concordant among identical twins.[169-171] Taken together, these studies suggest that there may be a genetic predisposition to alcoholism.

The identification of a genetically transmitted biologic marker (or markers) would be necessary in order to provide more definitive evidence that the etiology of alcoholism involves genetic factors. It is possible that brain function is involved in the genetic predisposition for alcoholism. The link between minimal brain dysfunction or hyperactivity in children and the subsequent development of alcohol abuse or alcoholism has often been noted.[164,172-175] For example, studies examining EPs in hyperactive children report a number of deficits that are similar to those seen in alcoholic adults. Hyperactive boys manifest reduced N1 amplitudes to all stimuli[176-178] as well as diminished P3 amplitudes to task relevant targets.[178,179] There is also evidence to indicate that brain EP wave forms are genetically determined. Monozygotic twins manifest EP wave forms that are as concordant with each other as are EPs obtained from the same individual tested twice.[180]

We have recently undertaken a major project to investigate the possibility that sons of male alcoholics manifest brain aberrations 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 electrophysiologic recordings from the sons of alcoholics (high risk) with age-and-education-matched sons of nonalcoholics (low risk). Children having a mother who abused alcohol are excluded from study so as to rule out any possible contribution to the results obtained from the effects of the fetal alcohol syndrome (FAS).

The results obtained thus far are striking. In one ERP study[157] we examined boys between the ages of 6 and 13 who had no prior experience with alcohol. We found that the group data of the high-risk sample were markedly different from those of the low-risk group. P3 components in the sons of alcoholics were

found to be significantly lower in amplitude than they were in the control boys. The P3 deficit was even more striking for a difficult task than for an easy task and was most marked at the parietal scalp lead. In addition, the group ERP wave form in sons of alcoholics was markedly similar to the ERP wave forms recorded in alcoholics. Factor analysis revealed that only the factor representing the P3 component was significantly different between the high- and low-risk groups. As only a small percentage of sons of alcoholics eventually become alcoholic, we examined the individual recordings to determine what percentage of the high-risk boys manifested these deficits. Of the 22 high-risk boys tested, eight manifested clear-cut ERP aberrations. None of the 22 low-risk subjects exhibited these ERP wave forms. This finding suggests that approximately 36% of the sons of alcoholics manifest an ERP abnormality. However, whether these ERP aberrations are in fact markers for a predisposition to alcoholism remains to be ascertained. By observing and testing the children in our sample each year it will be determined if those manifesting ERP differences are in fact those who develop problems with alcohol.

It should be noted that our results were obtained without the administration of alcohol. An interesting study conducted at the Salk Institute[49] has found that male college students with a family history of alcoholism respond differently than do matched controls to a challenge dose of placebo or alcohol.

Taken together, these studies suggest that individuals with a family history of alcoholism tend to manifest different ERP wave forms than do those without a family history of alcoholism. It should be noted, however, that nongenetic factors antedating alcohol abuse, and perhaps even predisposing to alcoholism, could influence the obtained results. It is well known that ingestion of alcohol by the mother during pregnancy increases the risk for offspring to develop FAS. Prenatal exposure to alcohol produces a myriad of brain abnormalities including delayed neural development in hippocampus, cerebellum, and cerebral cortex as well as aberrant neuronal and glial migration and synaptogenesis, and retards myelination of nerve fibers.[181–186] A study of BSPs in rat pups exposed to alcohol in utero indicates that BSPs are delayed during brain ontogenesis. Even though the BSP delays improved with continued development, they were still prolonged 70 days after parturition.[187] These results indicate either deficient or retarded myelination in the primary auditory pathway or impaired synaptic function as a result of prenatal alcohol exposure. However, one aspect of these results that is different from those obtained from alcoholics is that the rat pups manifested delays in wave I, which presumably reflect peripheral auditory nerve functioning, thereby suggesting that hearing loss was found in FAS pups.

It remains for future research to separate brain aberrations that precede alcohol abuse from those that are the consequence of chronic heavy drinking. It is not known at the present time whether innate differences in responsiveness to alcohol are associated with a predisposition to alcohol abuse. The preference

for alcohol varies between animal strains,[188] and differences in the neurophysiologic response to alcohol have been reported between rat strains.[6] As this review has indicated, humans also differ in their responsiveness to alcohol (e.g., augmenting/reducing, family history for alcoholism, flushers/nonflushers). For example, recent findings in Japan indicate that "flushers" (those who manifest an aversive physiologic reaction accompanied by vasodilatation after alcohol consumption) are more susceptible to delayed BSPs than are "nonflushers."[36] Individuals also differ with respect to the reinforcing properties of alcohol. Whether individuals more susceptible to the reinforcing effects of alcohol are more predisposed to drink problematically is, as yet, unknown. It remains for future research to determine whether the genetic markers of alcoholism involve innate differences in the response to alcohol, and whether such differences also relate to alcohol's differential reinforcing properties.

5. CONCLUSION

It is apparent from the foregoing review that the brain is a major target site for the actions of alcohol. Brain changes are associated with acute and chronic alcohol intake, alcohol withdrawal, and protracted long-term abstinence.

Despite the susceptibility of the brain to the deleterious effects of alcohol, the etiology of alcohol-related brain pathology has not yet been delineated. At present, the relative contribution of alcohol and acetaldehyde neurotoxicity, the indirect effects of alcoholization (e.g., anoxia), concomitants of withdrawal (e.g., stress, ischemia, anoxia), head trauma, and nutritional deficiencies on brain pathology and dysfunction are not known. There is evidence to suggest that alcohol intake in animals results in constriction of blood vessels in the brain and concomitant anoxia.[189] Perhaps it is only after protracted exposure to alcohol that permanent brain disruption occurs. Indeed, it is possible, as Horvath[190] has suggested, that there is a spectrum of brain pathology associated with alcoholism of which each of the factors mentioned may be critical for determining the type and severity of the brain disturbance detected. Furthermore, the recent evidence indicating that sons of alcoholics are at heightened risk for becoming alcoholic,[161] coupled with the finding that alcoholic individuals with or without a family history of alcoholism can be differentiated with respect to pattern of electrophysiologic responses,[49,157,191] suggests that there may be a genetic predisposition for some of the brain aberrations. Although the brain disturbances observed in chronic alcoholics are typically thought to represent the culmination of chronic heavy drinking, it is also possible that premorbid CNS factors may exist that render high-risk individuals more susceptible to alcohol-related brain pathology. Perhaps it is for this reason that given similar medical and drinking histories,

some individuals develop a myriad of severe CNS deficits, whereas others appear to be resistant to the deleterious actions of alcohol. Family history, however, is just one factor that may influence the individual's reaction to alcohol. The degree to which this and perhaps other factors interact to determine the overall response to alcohol remains to be ascertained.

Although the etiology of alcohol-related brain pathology is not entirely understood, there is increasing awareness of the patterns of brain deficits that either accompany or are consequential to alcoholism. This progress has been primarily facilitated by the application of computer technology for clinical and laboratory measurement. These computerized techniques have revealed that alcohol-related brain pathology is not as localized as had been thought originally. Prior to the availability of CT scanning, it was hypothesized, based on neuropsychologic findings, that the right hemisphere was more disrupted than the left hemisphere by alcohol abuse.[192] However, it now appears from CT scan findings that the cortical shrinkage is bilaterally symmetrical.[14] From the use of EP techniques it has been found that the brain dysfunction is not limited to the neocortex as had heretofore been thought. Although the neocortex appears to be extremely vulnerable, evidence implicates other brain regions such as the brain stem and hippocampus as being particularly sensitive to the effects of alcohol.

With the application of computer-based CT scan and ERP measurements, it will be possible to clarify the neurophysiologic mechanisms and underlying anatomic substrates that are disrupted by chronic alcohol use. Further research is necessary to determine the susceptibility of various brain loci to the effects of chronic alcohol exposure. Related to this issue is the need to ascertain whether the manifest cognitive deficits lie along a continuum of impairment,[193–196] or whether the deficits comprise a qualitatively distinct spectrum of alcohol-related deficits.[190–197]

Finally, it is important to determine which aspects of CNS disturbance are the result of withdrawal phenomena and which represent other forms of brain dysfunction. Despite the overwhelming evidence indicating that subacute withdrawal symptomatology persists for a long period of time,[5,19,22–24,91] investigators still continue to examine alcoholics rather soon after the cessation of alcohol abuse. This issue assumes an even more critical importance when the question of reversibility of brain damage or dysfunction after prolonged alcohol abstinence is considered. It is often unclear whether the observed "reversibility" is due to the subsiding effects of withdrawal or to recovery from other forms of brain disruption, particularly during the first few weeks after alcohol cessation. Although some improvement has been noted on neuropsychologic, electrophysiologic, and neuroradiologic measures after prolonged abstinence, it is unknown whether complete recovery with continued abstinence can take place. Systematic longitudinal study of CNS changes during acute withdrawal and prolonged ab-

stinence can perhaps elucidate the brain aberrations that characterize the withdrawal syndrome as well as clarify the potential for recovery from alcohol-related CNS disturbances.

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