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CHAPTER 11

Brain Dysfunction and Alcohol

Bernice Porjesz and Henri Begleiter

State University of New York
Department of Psychiatry
Downstate Medical Center
Brooklyn, New York

INTRODUCTION

Chronic alcoholism is characteristically associated with a spectrum of brain disturbances ranging from the severe symptoms of the Wernicke-Korsakoff syndrome (Butters and Cermak, 1980; Victor *et al.*, 1971) to the more subtle, but nonetheless significant, cognitive disturbances characteristic of the majority of alcoholic patients. It has been recognized that in some alcoholics the brain damage may be so severe that it renders the individual ineffective as a member of society. Less clinically apparent forms of brain damage have long been suspected but overlooked because it was not possible to examine them with available techniques. In some individuals, subclinical signs of brain dysfunction may possibly be a significant factor impairing their ability to reduce their intake or abstain from alcohol and may account for such phenomena as loss of control.

For a variety of reasons, the nature of the development of alcohol-related brain damage or dysfunction is still ambiguous. The ingestion of alcohol has been shown to result in central nervous system (CNS) changes during acute and chronic intoxication and withdrawal; these CNS changes are quite long-lasting, and it is not known at present whether in fact they completely recover with prolonged abstinence. Although the brain has been found to be quite susceptible to the deleterious effects of alcohol, the exact consequences of alcohol (or acetaldehyde) toxicity and withdrawal phenomena on brain damage or dysfunction and their interaction with repeated alcohol exposures are not known at the present time. The role of other possible contributing factors such as premorbid brain dysfunction, genetic factors, liver pathology, age of onset of alcohol abuse, and nutrition is largely unknown.

In recent years, some of these issues have been pursued with extensive animal experimentation investigating the effects of chronic alcohol intake on neurophysiological brain function (Altshuler *et al.*, 1980; Begleiter, DeNoble, and Porjesz, 1980; Siggins and Bloom, 1980; Walker *et al.*, 1981). It is evident that our knowledge of alcohol-related brain dysfunction will be significantly advanced with the use of laboratory animal studies. However, a complete understanding of the alcohol-related neuropathological findings and clinical symptoms cannot be entirely elucidated without careful neurobehavioral investigations of brain dysfunction in alcoholic patients. The major difficulties in conducting studies of alcohol-related brain dysfunction in man are due primarily to the relative inaccessibility of the human brain to direct study during life.

The recent development of advanced computer technology has made it possible to investigate structural (computerized tomography) and functional (evoked potential) brain deficits in chronic alcoholics with noninvasive techniques. These techniques permit an examination of more subtle forms of brain damage and/or dysfunction that had heretofore been unobtainable. These subtle forms of brain damage are important to assess, and their presence and early detection may alter prognosis and treatment.

The present chapter will review the recent findings of brain dysfunction in chronic alcoholics assessed with these sophisticated techniques. The first section deals with the reported incidence of various types of structural brain changes in chronic alcoholics, their relationship to neuropsychological assessment, and their potential reversibility in abstinent alcoholics. The second section deals with the effects of alcohol on the brain as determined by various evoked potential techniques.

These techniques can assess the level of brain functioning from peripheral end organ functioning to higher integrative processes. This section is subdivided into two major subsections dealing respectively with acute and chronic effects of alcohol intake. The first of these subsections examines the effects of acute doses of alcohol on brain functioning in healthy nonalcoholics, with the use of various evoked potential techniques. The second subsection addresses the assessment of brain dysfunction in chronic alcoholics with the use of the same electrophysiological probes. This section is further subdivided into three subtopics, each dealing with different postwithdrawal periods following alcohol abuse, namely short-term abstinence, long-term abstinence, and recovery.

STRUCTURAL BRAIN DAMAGE

Introduction

Brain damage has been diagnosed in alcoholics on the basis of a number of techniques; morphological changes have been directly demonstrated with the use of neurohistology (autopsy) and indirectly observed with the use of pneumoencephalography. Most recently, the nonintrusive methods of neuroradiology (computerized axial tomography or CT-Scan) have been widely used to assess structural changes in the brains of alcoholics. This section will discuss the findings of morphological brain changes in chronic alcoholics with each of these methods and their potential significance.

Incidence of Brain Damage

Autopsy

Ever since Courville's (1955) early autopsy examinations of the brains of chronic alcoholics, cortical atrophy and diffuse cell loss, particularly the dorsolateral convolutions of the frontal lobes, as well as ventricular dilation have been reported. Lynch (1960) corroborated Courville's postmortem findings, using light microscopy techniques; he estimated cortical cell loss to be as high as 20 to 40 percent of the total neuronal population. However, he found that cortical atrophy was not confined to the frontal lobes. Atrophy has been generally found to be more pronounced in alcoholic dementia than Korsakoff's psychosis, although some instances of cortical atrophy at autopsy in Korsakoff patients have been reported. Victor *et al.* (1971) reported that 25 percent of Korsakoff patients manifested cortical atrophy, whereas Neuberger

(1957) reported the incidence to be about 50 percent in chronic alcoholics. Korsakoff patients have been reported to exhibit only the same incidence of prefrontal cortical atrophy as age-matched controls (Angelergues, 1969; Brion, 1969; Victor *et al.*, 1971). Widespread damage has been reported to be present in at least two diencephalic brain regions, (1) the mamillary bodies of the hypothalamus (a major recipient of hippocampal output) (Angelergues, 1969; Brion, 1969; Talland, 1965) and (2) the medial and anterior portions of the thalamus (particularly dorsomedial nucleus). These diencephalic structures have been implicated in various memory disorders, including Korsakoff's syndrome (Butters and Cermak, 1980).

Pneumoencephalography (PEG)

Numerous pneumoencephalographic (PEG) studies have also reported a high incidence of cerebral atrophy in chronic alcoholics (Brewer and Perrett, 1971; Carlsson *et al.*, 1970; Ferrer *et al.*, 1970; Iivanainen, 1975; Lafon *et al.*, 1956; Ledesma-Jimeno, 1958; Lereboullet *et al.*, 1956; Postel and Cossa, 1956; Riboldi and Garavaglia, 1966; Tumarkin *et al.*, 1955). In one early PEG study, Tumarkin *et al.* (1955) examined a small sample ($n = 7$) of young alcoholics ($\bar{X}$ age 32) who had been drinking an average of 11 years. All seven patients showed signs of cortical atrophy, and ventricular enlargement was present in four (57 percent). In another early study, Lereboullet *et al.* (1956) stressed the similarity in clinical appearance between frontal lobe patients and chronic alcoholics. More recently, however, Haug (1968) reported that only half of the alcoholics who manifested cortical atrophy displayed signs of frontal lobe damage. Approximately 75 percent of 60 consecutive hospital admissions for alcoholism exhibited some atrophy 2–4 weeks after admission; the extent of atrophy was found to be related to the duration and amount of alcohol abuse and was more severe in patients who had delirium tremens. Similarly, Ohara and Homma (1974) found that the more heavily an alcoholic drinks, the larger the lateral ventricles and hence the greater the cerebral atrophy. They observed enlarged lateral ventricles in alcoholics, particularly when delirium tremens, Korsakoff's psychosis, and alcoholic hallucinosis were present, but failed to differentiate among the three, possibly separate entities on the PEG.

Brewer and Perrett (1971) investigated cortical and ventricular damage among "alcoholics" and "heavy social drinkers" (3 liters of beer or its equivalent per day). The degree of cerebral atrophy was assessed using several different measures (width of frontal and parietal sulci,

and the septum caudate line). Cortical atrophy was found in 30 out of 33 patients (91 percent), and enlarged ventricles were found in 24 out of 33 patients (73 percent). Only two patients were found to have normal PEGs. Frontal atrophy was found to be most common, occurring in 28 out of 30 patients with cortical atrophy (93 percent); parietal atrophy was also commonly found in 21 out of 30 patients with cortical atrophy (67 percent). Nineteen of the patients with parietal involvement also showed signs of frontal involvement. This study emphasizes the prevalence of brain damage and dysfunction in alcoholics, and even perhaps in regular social drinkers, in whom brain damage would not be likely to be suspected. Brain dysfunction has recently been reported in social drinkers (Parker and Noble, 1977) on the basis of neuropsychological tests; these studies indicate that the amount of alcohol per sitting is critical in determining degree of dysfunction.

Computerized Axial Tomography (CT-Scan)

Most recently, several laboratories throughout the world have turned to the technique of computerized axial tomography (CT-Scan) to investigate brain damage in alcoholics. In one of the first studies to use this technique in hospitalized alcoholics, Fox *et al.* (1976) reported significantly increased ventricular size in the alcoholic patients. These investigators reported the incidence of ventricular enlargement to occur in 33 percent of their patient group. The degree of concomitant enlargement of cerebral cortical sulci was not determined, as only 2 out of 12 patients (16.67 percent) exhibited clear-cut enlarged cortical sulci. Although the patients were evaluated as "normal" at discharge from the hospital, level of brain dysfunction was not measured.

Recent Swedish studies (Bergman *et al.*, 1977, 1980a; Bergman, Idestrom, and Borg, 1980) are investigating brain damage in chronic alcoholics with the CT-Scan. Bergman *et al.* (1977) reported that 60 percent of the patients showed "clear-cut" to "highgrade" brain damage, while only 8 percent showed none. Ninety-five percent had widened parietal sulci, and 69 percent of these had additionally widened frontal sulci. Widened sulci occurred more frequently over frontal and parietal areas than occipital (22 percent). In agreement with Fox *et al.* (1976), the same percentage of patients (33 percent) manifested ventricular enlargement. However, Bergman *et al.* (1977; Bergman, Idestrom, and Borg, 1980) reported that the incidence of cortical atrophy is greater than that of ventricular damage in chronic alcoholics and that they seem to be independent phenomena.

Similarly, an ongoing series of CT-Scan studies of chronic alcoholics

at the Addiction Research Foundation in Canada (Carlen *et al.*, 1976, 1978; Carlen and Wilkinson, 1980; Wilkinson and Carlen, 1980a,b) have revealed cerebral atrophy in all cases. In direct agreement with Bergman *et al.* (1977, 1980a), this group of researchers has found a greater degree of cortical than ventricular atrophy in chronic alcoholics in all their studies.

Similar results have recently been reported by Ron *et al.* (1978). They found that 65 percent of their sample of alcoholics showed radiological evidence of brain damage on the CT-Scan. In agreement with the studies at the Karolinska Institute in Sweden and Addiction Research Center in Canada, they found that the incidence of cortical atrophy alone was three times more frequent than ventricular enlargement alone, with 25 percent of the patients manifesting both cortical and ventricular enlargement.

Recent radiological work in Australia by Cala (Cala *et al.*, 1978, 1980; Cala and Mastaglia, 1981) corroborates pneumoencephalographic (Brewer and Perrett, 1971; Haug, 1968) and CT-Scan (Bergman *et al.*, 1980a; Bergman, Idestrom, and Borg, 1980; Carlen *et al.*, 1978; Carlen and Wilkinson, 1980; Ron *et al.*, 1978, 1980; Wilkinson and Carlen, 1980a, 1980b) findings of cortical atrophy and indicates cerebellar atrophy as well. Of 26 heavy drinkers, 19 were found to have cortical atrophy (73 percent). Of these, 13 had severe, 1 had moderately severe, and 6 had mild cortical atrophy.

In agreement with other investigators (Bergman *et al.*, 1977; Bergman, Idestrom, and Borg, 1980; Carlen *et al.*, 1975; Carlen and Wilkinson, 1980; Ron *et al.*, 1978; Wilkinson and Carlen, 1980a, 1980b), Cala found the incidence of cortical atrophy to be greater than ventricular enlargement. However, whereas Bergman *et al.* reported that cortical and ventricular atrophy appeared to be independent phenomena, Cala *et al.* (1978) report that ventricular enlargement was present together with cortical atrophy in the more advanced cases. They do not report any signs of ventricular dilation without cortical atrophy, and their results suggest a continuum, beginning with cortical atrophy and then leading to more central brain involvement with continued drinking. Furthermore, Cala (Cala *et al.*, 1978; Cala and Mastaglia, 1981) reported that cortical atrophy was diffuse, being more pronounced in frontal areas, with particular involvement of the cingulate gyrus. We have made similar observations of global atrophy with a preponderance of frontal atrophy in our abstinent alcoholic patients (Begleiter, Porjesz, and Tenner, in preparation). Despite neuropsychological evidence implicating more brain damage related to alcoholism in the right hemisphere, Cala *et al.* (1978) find that the damage is symmetrically

distributed in both hemispheres. Sixteen of the 19 alcoholics with evidence of cortical atrophy in Cala's sample also showed signs of cerebellar atrophy (84 percent). There were also three cases with mild cerebellar atrophy without accompanying cortical atrophy. A poor correlation existed between atrophy and neurological deficits. More recently, Cala (Cala *et al.*, 1980) replicated her results with a considerably larger sample of alcoholics ($n = 73$). Although cortical atrophy was found to be global and symmetrical, it was most pronounced over frontal areas with temporal areas being the second most affected. As in her previous study, central atrophy was never seen without cortical atrophy, and approximately half of the patients showed both cortical and central atrophy. Years of constant drinking were found to correlate with atrophy and age (as age and years of drinking were correlated). Cala and Mastaglia (1981) describe a progression of brain changes with age. In younger alcoholics, they report frontal atrophy with widened interhemispheric fissure. We have made similar observations of frontal interhemispheric atrophy in young alcoholics (Begleiter, Porjesz, and Tenner, in preparation). With age, the process includes temporo-parietal and occipital sites. Patients with Wernicke-Korsakoff Syndrome manifested more cerebellar and brain stem atrophy, which invariably involved marked supratentorial atrophy. In fact, Cala and Mastaglia (1981) report that they rarely observe cerebellar atrophy without accompanying supratentorial atrophy.

A number of studies in Germany have also revealed cortical atrophy in a vast majority of alcoholic patients (Gall and Becker, 1978; Gall *et al.*, 1978; Gotze *et al.*, 1978). In the study by Gotze *et al.* (1978) they found that as high as 96 percent of 50 chronic alcoholics under the age of 55 showed signs of cerebral atrophy with both cortical and subcortical signs being present in most cases. In agreement with Cala *et al.* (1978), cerebral atrophy was related to the subject's age and duration (not severity) of alcohol abuse. Similarly, degree of cortical atrophy has been reported to correlate with length of drinking history and age in a number of other laboratories (Bergman *et al.*, 1980b; Ron *et al.*, 1978; Wilkinson and Carlen, 1980a). However, the effects of length of drinking on CT-Scan measures are difficult to separate from those of age because the older alcoholics tend to have longer drinking histories. In fact, age seems to correlate more significantly with measures of CT-Scan damage (anterior brain index, width of third ventricle, cortical changes) than duration of abuse (Bergman *et al.*, 1980b). When age is partialled out, only the width of the third ventricle still correlates (although weakly) with length of drinking history (Bergman *et al.*, 1980b). Similarly, Wilkinson and Carlen (1980b) report that in non-

amnesic alcoholics, CT-Scan measures correlate with age. The relationship between degree of cortical atrophy on CT-Scans and age in alcoholics (Bergman *et al.*, 1980a,b; Cala *et al.*, 1978; Ron *et al.*, 1978; Wilkinson and Carlen, 1980b) make it difficult to assess aberrant levels of brain damage. As cortical atrophy has been shown to correlate with age in nonalcoholic samples (Earnest *et al.*, 1979; Gonzalez *et al.*, 1978), normative data are necessary for each age group, as a standard against which to determine what constitutes a pathological degree of atrophy. This lack of normative data constitutes a major problem in assessing CT-Scan results. Whereas formerly it had been considered sufficient to exclude patients over the age of 55–60 to control for age as a factor, recent CT-Scan investigations with alcoholic subjects have yielded rather surprising degrees of cortical atrophy at relatively young ages (Bergman, *et al.*, 1980b; Begleiter, Porjesz, and Tenner, in preparation; Lee *et al.*, 1979; Wilkinson and Carlen, 1980b). Only Hill *et al.* (1979) do not report a high incidence of atrophy in young (25–45 years) alcoholics. Lee *et al.* (1979) find a higher than expected percentage of young alcoholics (21–35) with atrophy (~49 percent). While Wilkinson and Carlen (1980b) note a correlation between age and degree of atrophy in nonamnesic alcoholics, their young alcoholics still manifest a high degree of sulcal width when compared to controls. Similar findings have been reported by Bergman *et al.* (1980a,b) in larger samples of alcoholics. These investigators report that 46 percent of young (20–29 year old) alcoholics manifest clear-cut or high-grade cortical changes.

Despite the tremendous advantages in the noninvasive CT-Scan technique over previous techniques to assess brain damage (e.g., pneumoencephalogram), it is still fraught with many problems. These problems are most apparent when comparisions are made across different laboratories. There is a lack of standardization in all aspects of CT-Scan methodology from data acquisition to measurement techniques. Although the basic CT technique is fairly similar across laboratories, different brain loci are often measured to assess atrophic changes. Even when the same brain structures are examined to assess brain damage, the diagnostic criteria vary greatly across laboratories; for example, ventricular enlargement can be obtained by measuring the width, area, volume, or various ratios of the ventricles, or just on the basis of a subjective clinical rating.

Whereas earlier investigations of brain damage in chronic alcoholics reported higher percentages of ventricular enlargement than widening of cortical sulci (Haug, 1968), the more recent CT-Scan findings have all generally observed a much higher incidence of cortical than ventricular damage (Begleiter, Porjesz, and Tenner, in preparation; Bergman

et al., 1977; Bergman, Idestrom, and Borg, 1980; Cala *et al.*, 1978; Carlen *et al.*, 1976, 1978; Carlen and Wilkinson, 1980; Ron *et al.*, 1978; Wilkinson and Carlen, 1980a, 1980b). It must be remembered that the earlier studies used pneumoencephalographic techniques which did not always permit accurate sulcal visualization.

However, caution is suggested in evaluating CT findings today, since similar intrinsic difficulties with the technique may exist. While the cortical sulci and ventricles can be well visualized on the CT-Scan, other brain sites, notably hippocampus, known to be severely affected by alcohol (Begleiter, DeNoble, and Porjesz, 1980; Riley and Walker, 1978; Walker *et al.*, 1980) cannot be adequately seen. Therefore, it is premature to conclude that cortical atrophy is more prevalent than subcortical damage on the basis of the CT-Scan.

The significance of cortical atrophy itself is unclear at the present time. The underlying neuropathology, pathophysiology, pathogenesis, and so forth of alcohol-related sulcal enlargement are still unknown and require further investigation. The term *brain shrinkage* instead of atrophy has recently been suggested by Ron *et al.* (1979, 1980) to describe the CT results. This descriptive term is being readily adopted by other investigators (Cala and Mastaglia, 1981) until the nature of these radiological findings can be elucidated.

The Relationship between Structural Brain Damage and Neuropsychological Tests

Prior to the advent of the CT-Scan, investigators using the PEG were interested in assessing the relationship between brain atrophy and neuropsychological tests (Brewer and Perrett, 1971; Ferrer *et al.*, 1970; Haug, 1968; Tumarkin *et al.*, 1955). These early investigators found correlations between cortical atrophy and Digit-Symbol and Digit-Span Wechsler–Bellevue subtests (Tumarkin *et al.*, 1955), Grassi Block Substitution Test and Minnesota Perception Diagnostic Test (Ferrer *et al.*, 1970), and the WAIS and Benton Visual Retention Test (Brewer and Perrett, 1971). A more recent attempt to investigate this relationship between chronic alcoholism, brain damage (PEG), and neuropsychological dysfunction was undertaken by Brewer and Perrett (1971). Intellectual dysfunction was found to be more closely related to cortical atrophy ($p < 0.01$) than ventricular damage ($p < 0.05$).

Another study attempting to establish the relationship between brain damage and neuropsychological dysfunction was undertaken by Horvath (1975). He extensively examined 100 out of 1100 alcoholics

who were diagnosed as having dementia (chronic organic brain syndrome), based on memory and intellectual and personality deficits. These patients were evaluated using air-encephalography, psychometric batteries, EEG, CSF, and skull X-rays. A comparison of the demented with the nondemented alcoholics indicated no difference in the incidence and degree of liver disease. Demented alcoholics were found to have longer drinking histories and higher daily alcohol consumptions than nondemented alcoholics. Sixty-two demented patients underwent air-encephalography examinations which revealed ventricular enlargement (especially of the lateral ventricles), widened cortical sulci, and in some cases atrophy of the cerebellum (particularly the upper vermis). When this latter symptom was present, it was associated with trunkal ataxia. However, correlations between severity of dementia and degree of cerebral atrophy were low. On psychometric and clinical evaluations, patients tended to cluster around different types of deficits rather than exhibiting homogeneous signs of dysfunction. Therefore, Horvath (1975) subdivided his group of demented alcoholics into several subgroups depending on their type of impairment. His group of "simple dementia" ($n = 12$), characterized by poor reasoning and memory for recent events, depression, and apathy, did not suffer from malnutrition, Wernicke's encephalopathy, or neuropathy. Both daily alcohol consumption and incidence of delirium tremens were highest in this group. He categorized patients with Korsakoff's syndrome ($n = 20$) as distinctly separate from those with other forms of dementia; these patients manifested Wernicke's encephalopathy, neuropathy, and confabulation. Malnutrition was evident in 80 percent, and most of them exhibited some cortical signs in addition to the pure diencephalic amnesic syndrome characterizing this group. His other groups included frontal, parietal, fronto-parietal and global disorders. Thus, on the basis of Horvath's work, it appears that chronic alcohol abuse may lead to a broad spectrum of types of brain damage; their etiologies still remain to be determined.

Recent Swedish studies at the Karolinska Institute (Bergman *et al.*, 1977, 1980a) are exploring the relationship between brain damage and neuropsychological functioning, using computerized tomography to ascertain brain damage and a psychometric battery to assess brain dysfunction. Forty percent of the patients showed deficits on the Halstead Category Test. Interestingly, mental dysfunction (as assessed by the psychometric battery) was often unimpaired despite signs of ventricular and cortical changes. In contrast to Horvath (1975), correlations between type of brain damage and neuropsychological scores revealed significant relationships. However, it is uncertain whether

Horvath (1975) divided his psychometrically distinct groups into different types of brain damage or whether he simply correlated degree of brain damage with psychometric score. Bergman *et al.* (1977) found the Halstead Impairment Index to be indicative of cortical degeneration, while learning and memory dysfunction (Claesson–Dahl verbal learning and memory for designs) reflected central brain degeneration. The most significant relationship was found between verbal learning and memory and morphological central changes. It is unclear whether any attempt was made to analyze different types of cortical damage—for example, frontal versus parietal in this study. More recently, Bergman, Idestrom, and Borg (1980) reported that frontal atrophy was more correlated with psychometric deficits than other cortical loci. However, this perhaps indicates that the neuropsychological tests used to assess level of functioning are particularly sensitive to frontal function.

Bergman *et al.* (1980a) conclude that in chronic alcoholics, cortical changes are associated with neuropsychological deficits, such as abstraction, while central changes are associated with learning and memory deficits. They postulate that these cortical deficits may either predate or occur early in chronic alcoholism, while central changes are postulated to result from many years of alcohol abuse. Furthermore, they suggest that rather than being a continuum, these are two separate consequences of alcoholism.

The relationship between neuropsychological test performance and brain damage is being investigated at the Addiction Research Foundation in Canada (Carlen *et al.*, 1976; Wilkinson *et al.*, 1976). In one of their earlier studies (Wilkinson and Carlen, 1980a) a group of 72 alcoholics who had been drinking a minimum of 10 years was studied using a test battery (consisting of the WAIS, Halstead–Reitan, and WMS) and their psychometric scores were related to their CT measures of atrophy. Whereas most investigators exclude patients with signs of brain damage and/or Wernicke–Korsakoff diseases, these investigators included a wider spectrum of alcoholics. Their sample consisted of patients initially presenting with Wernicke-Korsakoff syndrome, alcohol withdrawal, and chronic dementia, and they were studied for up to a year after hospital admission. On neurological and psychological tests, the patients manifested recent memory loss, cerebral-cortical deficits, cerebellar ataxia, and EEG aberrations. The alcoholics were separated into two groups on the basis of neurological tests, and it was found that the neurologically "impaired" group scored significantly more poorly on all measures. However, both groups had enlarged sulci and ventricles when compared to a group of normal controls (nondemented, age-matched Ss). Of the 72 alcoholics, 15 were diagnosed as having

Wernicke–Korsakoff's Syndrome, and these were found to have lower memory quotient scores but the same verbal and performance scores as non-Wernicke Ss. This memory deficit would be expected on the basis of diagnostic criteria for Wernicke–Korsakoff Syndrome. Oddly enough, in terms of CT results, the alcoholics with amnesic deficits displayed significantly more sulcal, but not ventricular enlargement (Wilkinson and Carlen, 1980a, 1980b). They postulate that perhaps thalamic lesions are present but not detectable on the CT-Scan in this group. However, the question of whether brain morphology (as assessed by CT-Scans) is related to psychometric assessment is still equivocal. Wilkinson and Carlen (1980b) have recently reported that while neuropsychological test score (Halstead–Reitan Impairment Index) correlates with cortical atrophy (as had been found by Bergman *et al.*, 1977, 1980a; Bergman, Idestrom, and Borg, 1980), age correlates even more highly with brain morphology in nonamnesic alcoholics.

However, Ron *et al.* (1978) report that no specific intellectual deficits were found to correlate with different types of brain abnormalities. Since the psychometric tests used to evaluate intellectual deficits were different from those used by the other investigators (the Halstead–Reitan Impairment Index was not used), the results of these neuropsychological findings cannot be compared across laboratories.

The relationship between neuropsychological function and brain damage was also investigated by Cala *et al.* (1978). They found no relationship between total WAIS Score and cortical atrophy. However, certain of the subtests (those tapping visuo-spatial and visuo-motor functions) were found to correlate significantly with degree of atrophy (Digit-Symbol, Block Design, and Object Assembly). Verbal and memory skills seemed to be unimpaired in most of the subjects, while the neuropsychological functions most affected were the so-called right-hemisphere functions. Cortical atrophy was bilaterally symmetrical and diffuse, not being selectively more atrophic in the nondominant hemisphere. Cognitive impairment was not related to specific locus of atrophy, but rather the greater the atrophy, the greater the cognitive deficit. While the cognitive impairment was specific (e.g., right hemisphere), the cortical atrophy was symmetrical and diffuse, although the frontal lobes were most affected, followed by temporal, parietal, and occipital.

While many laboratories throughout the world have attempted to relate brain damage measures with neuropsychological test performance, these studies have resulted in conflicting reports that can be partially explained by differences in methodologies. Neuropsychological tests and measures of brain damage are often different across labora-

tories. Thus, the brain functions that are correlated with different aspects of brain damage may vary in different investigations. Despite significant correlations relating atrophy on CT-Scans with neuropsychological test scores in abstinent alcoholics (Bergman *et al.*, 1980a; Wilkinson and Carlen, 1980b), most of these relationships dissipate once age is partialled out.

Furthermore, the relationship between brain structure and behavior remains a troubling and elusive problem. Gonzalez *et al.* (1978) has found a surprisingly poor correlation between neuropsychological deficit and atrophy in 100 normal volunteers. Thus, as the relationship between cortical atrophy and neuropsychological performance is at best tenuous, it leaves many questions about the utility of trying to relate these measures to each other at the present time. Many of the problems lie in the nature of the neuropsychological tests themselves; for example, it is almost impossible to equate so-called right and left hemisphere tasks. One of the more obvious problems is the degree of learning involved, with left-hemisphere tasks very often being overlearned and right-hemisphere tasks being more novel. As alcoholics have more problems with "fluid" as opposed to "crystalized" intellectual functions (Overall *et al.*, 1978), the often reported selective right-hemisphere deficit may be a function of the inability to solve unfamiliar problems. This may explain the finding of Cala (Cala *et al.*, 1978; Cala and Mastaglia, 1981) who reported that although so-called right-hemisphere neuropsychological functioning was more impaired in alcoholics, atrophic changes were symmetrical over the two hemispheres.

Furthermore, with each technique there is a tendency to focus on and measure those aspects that are most easily observed. However, what can easily be visualized on the CT-Scan or assessed with neuropsychological tests may not be the most clinically relevant information.

The relationship between structure and function is one of the most elusive in brain research. It is now well established that severe cortical atrophy is not necessarily related to neuropsychological or behavioral aberrations (Earnest *et al.*, 1979; Ramani *et al.*, 1979). Therefore, it should not be surprising that the relationship between CT-Scan measures and neuropsychological test scores in chronic alcoholics is at best weak.

Reversibility of Structural Damage

An extremely important and clinically relevant issue in the area of alcohol-related brain damage and dysfunction is the possibility that brain damage and/or dysfunction is reversible with prolonged absti-

nence. The question of reversibility of dysfunction in the alcoholic population has received a considerable degree of attention in the neuropsychological literature. In general, neuropsychological studies dealing with reversibility indicate improvement of psychomotor and intellectual functioning during the first three weeks of abstinence (Page and Linden, 1974). However, whether further improvement continues beyond that time or whether level of functioning ever fully returns to normal is still an unresolved question.

The reversibility of alcohol-related brain damage assessed with PEG techniques has not been thoroughly investigated. Studies utilizing the PEG often study patients at different points in time after alcohol abuse. One attempt to study reversibility and PEG was undertaken by Ledesma-Jimeno (1958). Five patients were studied after abstinent periods ranging from 2 months to two years. The degree of cerebral atrophy remained unchanged, and it was concluded that no reversibility occurs.

However, some reversibility of cortical atrophy with prolonged abstinence from alcohol has been reported using the CT-Scan. This was first reported by Carlen *et al.* (1978) in a small sample of patients. Half of the patients (4 out of 8) showed some improvement on repeated CT-Scans. Although the exact times of the scans varied from patient to patient, they were taken at approximately one month and eight months after alcohol withdrawal for each patient. As reported in their previous studies (Carlen *et al.*, 1976), the percentage decrease of cortical atrophy was greater than that of ventricular atrophy. Improvement in cerebral atrophy was not always accompanied by clinical improvement. What factors differentiated the patients who improved from those who did not remains to be clarified. Half of the patients in each category improved significantly on psychological testing, clinical evaluation, and neurological assessments anywhere from the first few weeks to the first few months of abstinence. It should be noted that although improvement in atrophy was reported in half of the patients, the patients did not recover completely and did not reach normal levels of cortical and ventricular size for their age. Thus, all patients still exhibited positive CT-Scans as late as 8 months after withdrawal. This result is similar to findings obtained with neuropsychological tests, wherein test scores, although improved, still remain below the norms (Carlsson *et al.*, 1973; Clarke and Haughton, 1975; Jonsson *et al.*, 1962; Page and Linden, 1974).

Since Carlen's original study of reversibility of brain damage as assessed by CT-Scans, many laboratories throughout the world are currently investigating this issue of long-term reversibility (Begleiter, Porjesz, and Tenner, in preparation; Carlen and Wilkinson, 1980;

Gotze *et al.*, 1978; Ron *et al.*, 1980). Ron *et al.* found some improvement in cortical and ventricular measures following 31–91 weeks of total or partial abstinence in a small sample of alcoholics. Alcoholics who continued to drink, however, manifested somewhat more severe cortical atrophy with continued drinking, but no change in their ventricle/brain ratios. Carlen and Wilkinson replicated their initial findings of reversibility of cortical sulcal and ventricular size in a larger sample of patients. In addition, they reported a negative correlation between the age of the patient and the degree of reversible atrophy. Thus, the degree of recovery is greater in younger abstinent alcoholics than older abstinent alcoholics. In one published report dealing with the question of reversibility in Germany (Gotze *et al.*, 1978), CT measures were obtained in 10 patients during acute withdrawal and following four weeks of abstinence. No changes in CT were noted, and the investigators concluded that cerebral edema was not detected. However, although on the surface these findings seem to contradict those of Carlen *et al.* (1978), the repeated scan in this study was taken at approximately the time of the first scan in the Carlen study. Thus the "transitory changes" Gotze refers to may still be present. In our own laboratory (Begleiter, Porjesz, and Tenner in preparation), we are examining patients with repeated CT-Scans who have been abstinent from alcohol for as long as four months and have not as yet seen any substantial or significant signs of reversible cortical atrophy in most patients.

The so-called reversibility of cerebral atrophy is as yet still an unresolved issue. Problems in technique of measurement, time of assessment, and test–retest positioning, and so forth, make it difficult to compare results of repeated scans within and across laboratories. It is difficult to place a patient in the identical position twice, and the slightest discrepancy in position will yield somewhat different cuts. It is possible that CT-Scans obtained early in the course of recovery (3 weeks) are indicative of concomitants of withdrawal rather than brain damage. In our laboratory, we have found that evoked-potential hyperexcitability in rats lasts as long as five weeks after withdrawal (Porjesz *et al.*, 1976; Begleiter and Porjesz, 1977); the persistence of this residual hyperexcitability was found to be related to the length of chronic alcohol use. Carlen *et al.* (1978) found that the earlier they had taken the first scan, the greater the improvement in atrophy. It is possible that initial brain dysfunction caused by withdrawal (hyperexcitability) was indistinguishable from other forms of brain damage and that improvement (due to dehydration, edema, etc.) was a subsiding of the hyperexcitability.

At present it is uncertain whether brain changes noted on CT-Scans in chronic alcoholics are reversible or not. The number of patients

reexamined with repeat scans remains very low. Furthermore, the significance of cortical atrophy and its so-called reversibility in terms of underlying neuropathophysiology remains to be determined. It is still inconclusive whether only concomitants of withdrawal are reversible following prolonged alcohol abuse or whether cortical atrophy represents more long-term brain damage. Aberrant fluidizing effects in membranes have been reported with chronic alcohol intake (Chin *et al.*, 1979), which may result in edema. Edema is seen following osmotic stress (Neuwelt *et al.*, 1980; Pollay, 1975; Rapoport, 1976), which may cause demyelination (Fiegen and Budzilovich, 1978, 1980; Kleinschmidt-DeMasters and Norenberg, 1981; Lewis, 1976; Yates, 1976). It is presently unknown whether "recovery" from brain damage following abstinence from alcohol represents changes in glial cells, regrowth of attenuated dendritic and axonal processes of cortical neurons, or water and electrolyte abnormalities (Carlen and Wilkinson, 1980). In discussing this issue, Carlen and Wilkinson (1980) suggest that increased CNS protein synthesis rather than rehydration accounts for this reversibility. They base this conclusion on a recent preliminary finding that ventricular volume decreases and mean brain density increases on repeat scans. However, it is possible that both the metabolic and morphological changes that occur with alcohol abuse may recover with prolonged abstinence.

Summary

Thus, taken together, the results of CT-Scan studies from many different laboratories concur that:

1. The majority of chronic alcoholics (>67 percent) manifest cortical atrophy (Begleiter, Porjesz, and Tenner, in preparation; Bergman *et al.*, 1977; Cala *et al.*, 1978, 1980; Cala and Mastaglia, 1981; Carlen and Wilkinson, 1980; Gall *et al.*, 1978; Gall and Becker, 1978; Gotze *et al.*, 1978; Ron *et al.*, 1978; Wilkinson and Carlen, 1980a, 1980b).
2. Cortical atrophy is more prevalent than ventricular atrophy in chronic alcoholics (Begleiter, Porjesz, and Tenner, in preparation; Bergman *et al.*, 1977; Cala *et al.*, 1978, 1980; Cala and Mastaglia, 1981; Carlen and Wilkinson, 1980; Gall *et al.*, 1978; Ron *et al.*, 1978; Wilkinson and Carlen, 1980a,b).
3. Atrophy is diffuse with a preponderance at frontal sites (Begleiter, Porjesz, and Tenner, in preparation; Cala *et al.*, 1978; Cala and Mastaglia, 1981; Gall *et al.*, 1978).
4. Length of drinking history and age correlate with atrophy (Cala

et al., 1978, 1980; Cala and Mastaglia, 1981; Gotze *et al.*, 1978; Ron *et al.*, 1978; Wilkinson and Carlen, 1978); however once age is partialled out, duration of abuse is essentially unrelated to CT-Scan findings.

5. Although there is a modest relationship between CT-Scan measures of brain damage and neuropsychological test scores, these relationships remain tenuous independent of age (Bergman *et al.*, 1980a; Ron *et al.*, 1978; Wilkinson and Carlen, 1980b).
6. Cortical atrophy or shrinkage on CT-Scan has been found to be partially reversible (Carlen *et al.*, 1978; Carlen and Wilkinson, 1980; Ron *et al.*, 1980) with continued abstinence.

EVOKED POTENTIALS

Introduction

As the previous section indicated, the assessment of structural damage in the brains of chronic alcoholics has been greatly facilitated by the use of the CT-Scan, indicating prevalent cortical atrophy, particularly over frontal areas (Begleiter, Porjesz, and Tenner, 1980; Bergman *et al.*, 1980a; Cala *et al.*, 1978, 1980; Cala and Mastaglia, 1981; Ron *et al.*, 1978; Wilkinson and Carlen, 1980a,b). However, this technique is limited in that it permits better visualization of some brain loci and hence can detect major morphological changes in certain brain areas (e.g., cerebral cortex) to the exclusion of others (brain stem). Furthermore, the CT-Scan provides a static picture of gross brain morphology, without providing information about underlying pathophysiology. The relationship between brain damage (as visualized in the CT-Scan) and level of brain functioning (as assessed by neuropsychological tests) remains tenuous (Lusins *et al.*, 1980). Neuropsychological tests, although helpful in assessing cognitive deficits in chronic alcoholics, are limited in that they must rely solely on behavior; with these tests, alcoholics are found to be deficient in abstraction and visual-spatial abilities. Yet the same behavioral deficits may well reflect the product of different complex neurophysiological processes or neuropathological deficits. Although it has become widely recognized that chronic alcoholics manifest brain dysfunction and/or damage, the nature and mechanisms of this dysfunction have not been clearly delineated.

With the advent of computers and the development of sophisticated mathematical techniques, it is now possible to obtain objective, quantitative neurophysiological data from the detailed analysis of evoked

potentials. The evoked potential (EP) or event-related potential (ERP) techniques offer a unique approach for assessing level of brain functioning because they permit the simultaneous observation of electrophysiology and cognition. The quantitative measurement of salient features extracted from EP or ERP recordings reflects various aspects of brain function related to integrative processes as well as the functional integrity of different neuroanatomical systems. These powerful EP techniques occupy the interface between cellular neurobiology and the behavioral sciences. An evoked potential is obtained by recording the time-locked brain electrical activity following the delivery of a discrete stimulus of any modality. The neuroelectric activity that is time-locked to the stimulus (evoked potential) is elicited with each stimulus presentation, while the background noise in which it is embedded is not time-locked. Signal-averaging techniques make it possible to extract the time-locked neuroelectric signal (evoked potential) from the background random noise, which cancels out under these procedures. These time-locked signals represent activity at neural generators from the peripheral end organ to higher integrative centers of the brain. Thus, with the use of these sophisticated neurophysiological techniques, the functional integrity of various systems of the brain (from the peripheral end organ to cortex) can be assessed.

ERP techniques have proved to be very valuable in indexing electrophysiological concomitants of information-processing tasks. ERPs have an advantage over neuropsychological tests in that they can be recorded in conjunction with behavior, or even when no behavioral response is required; they can be recorded to both attended and unattended stimuli. Thus, the ERP techniques are very sensitive indices of the functional integrity of the brain; they differ from the CT-Scan in that they reflect subtle changes in brain functioning without necessarily involving gross brain damage.

Recording electrical activity from the brain has proved to be the only technique that is sensitive to the various CNS dynamics reflecting alcohol-related effects, namely, alcoholization, tolerance, withdrawal, and long-term brain dysfunction (Begleiter and Porjesz, 1979; Zilm *et al.*, 1981). Recent evidence recording electrophysiological activity in animals and man at various stages of alcohol-induced dysfunction has indicated that the same evoked potential measure is an extremely sensitive indicator differentiating various aspects of alcohol-related changes.

Alcoholization is characterized by marked depressions in EP amplitude (Bierley *et al.*, 1980) and prolonged conduction velocities of the BSP (Chu *et al.*, 1978; Squires *et al.*, 1978a, 1978b). Chronic alcohol

intake is accompanied by EP amplitude reductions and BSP delays which are less pronounced when tolerance develops (Begleiter and Porjesz, 1977; Chu *et al.*, 1978; Porjesz *et al.*, 1976; Squires *et al.*, 1978a,b; Zilm *et al.*, 1981). These techniques are also very sensitive to withdrawal phenomena which are characterized by increased EP voltages and extremely shortened BSP latencies indicative of underlying CNS hyperexcitability (Begleiter and Porjesz, 1977, 1979; Chu *et al.*, 1978; Squires *et al.*, 1978a,b). Finally, long-term abstinence is marked by decreased EP amplitudes (hyporeactivity) and abnormally prolonged BSP latencies and conduction velocities (Begleiter, Porjesz, and Chou, 1981); the duration of these prolonged CNS disturbances and their potential recovery are not yet known.

This electrophysiological review will deal solely with the use of evoked potential techniques in assessing the effects of alcohol on the brain. For an extensive review of the effects of alcohol on EEG activity, the reader is referred to the chapter by Begleiter and Platz (1972) in Volume 2 of this series. The present review dealing with evoked potentials and alcohol will be divided into two major sections. The first section will deal with the effects of acute alcoholization and the second will deal with chronic alcoholization. The latter section will deal with the electrophysiological concomitants of short-term abstinence (withdrawal) and long-term brain damage and possible recovery separately. Each section and subsection will be further subdivided according to the EP technique used to assess brain functioning, namely, brain stem potential (BSP), pattern evoked potential (PEP), sensory evoked potential (EP), and event-related potential (ERP).

Acute Alcoholization

The effects of acute doses of alcohol on normal brain functioning have been investigated in an effort to ascertain some parallel between the effects of acute and chronic alcohol intake on the brain. The scalp evoked potential (EP) in man has been useful in examining this problem, since it can elucidate differential responsivities of brain loci to alcohol effects. By indicating the sites of action of acute doses of alcohol in the brain, possible loci of brain dysfunction resulting from chronic alcohol abuse can be indicated.

Auditory Brain Stem Potentials (BSP)

With the advent of the auditory brain stem potential (BSP) technique, it is now possible to investigate subcortical brain functioning with a noninvasive scalp electrode (Jewett, 1970; Jewett and Williston, 1971;

Sohmer and Feinmesser, 1967). These potentials consist of seven time-locked positive deflections that are considered to be "far-field" projections of neuroelectric activity occurring in the auditory pathway (Jewett and Williston, 1971; Plantz *et al.*, 1974). Neuropathological studies in animals and humans have postulated the origins of waves I–III as the auditory nerve, cochlear nuclei, and superior olivary nucleus of the medulla, respectively, while the later waves IV–VI are postulated to be generated in the nuclei of the lateral lemniscus, inferior colliculi, and medial geniculate bodies, or a summation of discharges from these structures (Buchwald and Huang, 1975; Jewett, 1970; Lev and Sohmer, 1972; Starr and Achor, 1975; Starr and Hamilton, 1976; Stockard and Rossiter, 1977). The neural sites responsible for the activity of peaks VI and VII are still uncertain at present. The latencies of each of these peaks, as well as central conduction time (the latency of each peak with respect to peak I) are extremely accurate in localizing sites of pathology from the peripheral end organ to the brain stem.

The acute administration of alcohol to rats and cats has been shown to slow the central conduction times of peaks III, IV, V, and VII (Chu *et al.*, 1978; Squires *et al.*, 1978a), but not the early peaks (I and II). This indicates that conduction times in more central structures (beginning at the level of the medulla) but not the auditory end organ are susceptible to alcohol-related slowing.

Similar findings of increased delays of peaks IV–VII but not peak I were reported of healthy human subjects administered acute doses of alcohol by the same investigators (Squires *et al.*, 1978b). Furthermore, they observed that the later peaks (V–VII) were delayed sooner after alcohol ingestion than the earlier peaks (III and IV), although this was not systematically examined. It should be noted that these postalcohol peak delays remained within the normal range for all subjects. The latency delays were found to parallel clinical signs of intoxication more than actual blood alcohol levels. Although different subjects received different doses of alcohol (0.55–1.65 ml/kg), the relationship between alcohol dose to BSP delays or time course of peak delays was not discussed and requires further investigation.

These results of prolonged peak latencies of waves III–VII but not peaks I and II of the human BSP with acute alcohol administration were replicated recently in Japan (Fukui *et al.*, 1981). Furthermore, these investigators found that subjects who manifested facial flushing in response to alcohol displayed significantly larger shifts in latencies of peaks III, V and VII than nonflushers, despite a lack of difference in blood alcohol levels between the two groups. The investigators postulate that the difference between the two groups is due to differ-

ences in blood acetaldehyde levels (which were not measured in this study).

Sensory Evoked Potentials (EP) (P1–N1–P2)

Over the past decade and a half, the effects of acute doses of alcohol on human sensory evoked potentials (EPs) recorded at the scalp have been investigated in an effort to determine selective brain sensitivites to alcohol. EPs have been recorded following acute alcohol administration in all sensory modalities, namely: auditory (Elmasian *et al.*, 1981; Flach *et al.*, 1977; Fukui *et al.*, 1981; Gross *et al.*, 1966; McRandle and Goldstein, 1973; Neville *et al.*, 1981; Pfefferbaum, Horvath, Roth, and Kopell, 1979, 1980; Wolpaw and Penry, 1978), somatosensory (Lewis *et al.*, 1970; Porjesz and Begleiter, 1973; Salamy, 1973; Salamy and Williams, 1973) and visual evoked potentials (Erwin and Linnoila, 1981; Lewis *et al.*, 1969, 1970; Pfefferbaum *et al.*, 1977; Porjesz and Begleiter, 1975; Rhodes *et al.*, 1975; Simpson *et al.*, 1981; Spilker and Callaway, 1969; Taghavy *et al.*, 1976).

The primary finding on which all of these studies concur is that alcohol ingestion produces a marked depression in the late (N1–P2) components occurring after 100 msecs (Fukui *et al.*, 1981; Erwin and Linnoila, 1981; Lewis *et al.*, 1969; Pfefferbaum *et al.*, 1977; Pfefferbaum, Roth, Tinklenberg, and Rosenbloom, 1979; Porjesz and Begleiter, 1975; Rhodes *et al.*, 1975; Salamy and Williams, 1973; Taghavy *et al.*, 1976). Whereas the late EP components are maximally reduced, early components (<100 msecs) are relatively resistant to the depressant effects of alcohol in all sensory modalities (Lewis *et al.*, 1970; Salamy and Williams, 1973; Porjesz and Begleiter, 1975; Rhodes *et al.*, 1975; Pfefferbaum, Roth, Tinklenberg, and Rosenbloom, 1979c).

Since the amplitude reduction in average evoked potentials observed after alcoholization could be the result of increased latency jitter or the direct result of decreases of the single evoked potentials constituting the average, Salamy (1973) and Salamy and Williams (1973) investigated this issue. They concluded that the amplitude depression of late components of the average EP primarily represents decreases in single EP amplitudes, rather than increased latency variability.

In the recording of EPs from scalp leads in man, it has been found that alcohol produces its maximal amplitude depression over association areas as opposed to primary receiving areas. This has been reported for somatosensory (Salamy and Williams, 1973) and visual (Lewis *et al.*, 1970; Porjesz and Begleiter, 1975) evoked potentials. Visual evoked potential (VEP) studies have indicated that central (Cz, C3, C4) but not

occipital (0z, 01, 02) scalp loci are sensitive to depression by alcohol of components occurring before 150 msecs (Lewis *et al.*, 1970; Pfefferbaum *et al.*, 1977; Porjesz and Begleiter, 1975). The early components (<75 msec) were found to be unaffected by alcohol at all scalp loci by all three groups of investigators (Lewis *et al.*, 1970; Pfefferbaum *et al.*, 1977; Porjesz and Begleiter, 1975). Components occurring after 165 msec are somewhat depressed by alcohol at occipital sites, but to less of a degree than central responses (Pfefferbaum *et al.*, 1977; Porjesz and Begleiter, 1975). These findings indicate that association areas are more sensitive to alcohol than primary receiving areas in the visual modality. The visual modality is ideal to investigate selective sensitivities of the brain to alcohol because its primary receiving area and the more anterior association areas are well separated.

The primary sensory cortex has also been found to be more resistant to alcohol effects than association cortex for somatosensory human EPs (Salamy and Williams, 1973). This has not been demonstrated for the auditory EP, possibly because of the proximity between scalp recording sites for auditory and association cortices. The resistance of the primary sensory cortex (somatosensory) to extremely high doses of alcohol (7g/kg) has been recently reported in monkeys (Hyvarinen *et al.*, 1978). These investigators demonstrated that even when the animal was completely nonreactive to its environment, strong responses persisted to the touching of the hand in adjacent somatosensory cortex. The posterior parietal association cortex was found to be more sensitive to alcohol than the adjacent primary somatosensory cortex. Within the association cortex, however, not all electrode sites were similarly affected by alcohol.

Taken together, these results suggest that different brain regions are differentially susceptible to the effects of alcohol, although it is conceivable that all brain areas are ultimately affected by extremely high doses. It has been suggested that the selective sensitivity of different brain regions to alcohol depends on the complexity of synaptic connections (Himwich and Callison, 1972; Kalant, 1975, Wallgren and Barry, 1970). There is a proliferating animal literature indicating that polysynaptic brain sites such as association cortices and reticular formation are most responsive to alcohol (Begleiter, DeNoble, and Porjesz, 1980; DiPerri *et al.*, 1968; Kalant, 1975; Klemm *et al.*, 1976; Perrin *et al.*, 1974).

The differential effects of alcohol on right and left hemispheres have been the focus of interest in EP research for the last decade. This has been an outgrowth of the neuropsychological findings indicating more deficits in so-called right hemisphere tasks in chronic alcoholics;

specifically, visual-spatial tasks are impaired while verbal abilities remain intact on neuropsychological tests. Because EPs recorded bilaterally to blank flashes tend to be larger over right then left hemispheres at both central (Lewis *et al.*, 1970; Rhodes *et al.*, 1975) and occipital locations (Porjesz and Begleiter, 1975), they have been postulated to be mediated by the nondominant hemisphere. However, these are extremely small interhemispheric amplitude differences that only occur in some subjects. Differences of this order of magnitude can be due to fluctuations in resistance, amplifier differences, slight differences in electrode placements at homologous sites, and so forth. In fact, a striking degree of interhemispheric symmetry has been reported between identical bilateral electrode placements in large samples of healthy subjects (Harmony *et al.*, 1973). Nevertheless, all studies examining the effects of acute doses of alcohol on hemispheric asymmetry (Lewis *et al.*, 1970; Porjesz and Begleiter, 1975; Rhodes *et al.*, 1975) concur that alcohol dissipates preexisting hemispheric asymmetry. However, right hemisphere responses are reduced to a greater extent than left, regardless of whether or not there are preexisting hemispheric differences in amplitude (Porjesz and Begleiter, 1975). 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 left hemisphere responses. This suggests a greater susceptibility of the right hemisphere to the direct depressant effects of alcohol, rather than to preexisting hemispheric differences. Perhaps this is due to greater blood flow in the right hemisphere than in the left (Carmon *et al.*, 1972) and may have little to do with cognitive interhemispheric differences (Dabbs, 1980). Similar results have been reported with cerebral blood flow studies (Berglund, 1981, Berglund *et al.*, 1980) indicating a greater alcohol effect in the right hemisphere.

However, these small interhemispheric differences in responsiveness to alcohol are rather insignificant when compared to the more striking differential susceptibility of different nonhomologous brain loci (e.g., central vs. occipital) to alcohol. In a study of bilateral cortical and occipital VEPs to alcohol, we found that the magnitude of depression of central responses far exceeded the depression at occipital sites, to a much greater extent than any difference in amplitude recorded across hemispheres (Porjesz and Begleiter, 1975). Not only were different brain loci differentially depressed by alcohol, but their rate of recovery varied as well. We found that whereas occipital responses recovered after two hours, central responses did not, suggesting that the greater the magnitude of alcohol-related depression, the slower the recovery (Porjesz and Begleiter, 1975). Thus, we found a striking degree

of symmetry in responsivity of VEPs obtained from homologous bilateral scalp locations in terms of the degree and time course of depression of the various components when compared to other scalp regions.

The time course and magnitude of maximal alcohol effect on EPs and their subsequent recovery are due in part to dose of alcohol administration and testing regimen. Low doses of alcohol (0.41 g/kg–0.82 g/kg) yielding BALs of 30–60 mg% have been found to have no significant effect on visual or somatosensory EPs, while high doses (1.23 g/kg) yielding BALs of 90 mg% significantly depressed amplitudes (Lewis *et al.*, 1969, 1970).

These findings were confirmed in a more recent study (Erwin and Linnoila, 1981), wherein it was reported that low doses of alcohol (0.5 g/kg) yielding a BAL of 33 mg% did not significantly change VEP amplitude. There was a direct relationship between the dose of alcohol and the VEP amplitude. A medium dose of alcohol (0.8 g/kg) yielding a BAL of 67 mg% decreased the amplitude 27 percent from baseline, while a high dose (1.2 g/kg) yielding a BAL of 107 mg% decreased the amplitude 39 percent. Similarly, Salamy (1973) has found that low doses of alcohol (50–65 mg% BAL) depress somatosensory EPs to less of an extent than do high doses (95–110 mg% BAL). Thus, the dose of alcohol administered is directly related to the blood alcohol level and the degree of amplitude depression (Erwin and Linnoila, 1981; Salamy, 1973; Salamy and Williams, 1973). In a study examining the relationship between BAL and EP amplitude over time (Salamy and Williams, 1973), it was found that the N1–P2 amplitude is directly related to the absolute level of BAL, regardless of whether it is on the rising or falling limb of the BAL curve. However, the relationship between the rate of change of BAL and EP amplitude, or whether the same BAL produced by different alcohol doses affects EP amplitude similarly, still remains to be elucidated. In our laboratory (Porjesz and Begleiter, unpublished observations), we have observed that N1–P2 amplitude depressions are more related to BAL than time after alcohol ingestion, thus corroborating Salamy's findings. However, we have observed a great deal of intersubject variability, in terms of peak BAL obtained with a single alcohol dose, the time after alcohol ingestion when the peak BAL is obtained, and the magnitude and time after alcohol of the greatest EP amplitude depressions. These individual differences may in part be accounted for by differences in food ingested prior to testing, genetic or constitutional differences (Neville *et al.*, 1981; Propping *et al.*, 1980). Recent evidence suggests that individuals with family histories of alcoholism respond quite differently to alcohol than do individuals

without such histories (Neville *et al.*, 1981). This suggests that in addition to absolute blood alcohol levels, other factors account for the degree of EP amplitude depression. These interesting findings suggest that heredity or genetic predisposition plays a part in an individual's responsiveness to alcohol.

Thus, there are many factors that can account for differences in results between individuals and across laboratories, namely: dose of alcohol administered, testing regimen, stimulus parameters, subject factors (genetic differences, constitutional differences, nutritional status, etc.), control (placebo) group or condition. This last factor requires special attention in explaining differences in results across laboratories. Since individuals vary greatly in their response to alcohol, the control condition is critical in determining the nature of the results. This variability across individuals points to the importance of using each subject as his own control in a placebo condition to control optimally for drug effects. While cross-sectional designs, (where different drugs or placebos are administered to different groups of subjects) do provide valuable information, they require the use of large sample sizes because of intersubject variability, and within-subject designs may be superior. Another important aspect of drug studies is the predrug baseline, which provides a measure of current level of functioning and normal trial-to-trial variability without a drug effect. However, while the predrug baseline is important, it is not sufficient if it is the only control condition used in the EP experimental paradigm. Unfortunately, it is the same late components (N1–P2) that are most sensitive to alcohol that habituate most over time; therefore, the amplitude of N1–P2 is expected to decrease over time regardless of whether alcohol is administered. This makes interpretation of results rather difficult and perhaps explains the unusual finding of McRandle and Goldstein (1973), who found increases in N1–P2 amplitude following alcohol administration. Thus, the optimal alcohol design is one in which predrug baselines are obtained each day prior to the administration of a particular dose of alcohol or placebo and the same experimental procedure is followed under all conditions in the same subject.

Information Processing and ERPs (N1 + P3)

N1–P2. In the foregoing review, we have only dealt with studies that have required normal subjects to be passively attentive to stimuli while under the influence of alcohol. However, variations in other uncontrolled factors besides the alcohol effects may be involved in determining the results. Thus, for example, attentional factors cannot

be ruled out as interacting with alcohol effects to account for EP amplitude decrements. Many brain loci (e.g., association cortices) which are susceptible to alcohol's depressant effects are also those which may be associated with attentional factors. Furthermore, the same EP component (N1–P2) that is significantly depressed by alcohol is most sensitive to attentional manipulation.

Recently, investigators have attempted to separate the attentional factors from alcohol effects with the use of ERP techniques. These techniques require the subject to be actively engaged 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 using visual and auditory target selection tasks (Kopell *et al.*, 1978; Neville *et al.*, 1981; Obitz *et al.*, 1977; Pfefferbaum *et al.*, 1980; Porjesz and Begleiter, unpublished; Rhodes *et al.*, 1975), as well as with the use of a visually presented Sternberg memory retrieval paradigm (Roth *et al.*, 1977). All of these experimental paradigms require the subject to be actively attentive. The target-selection tasks require the subject to detect a designated, rarely occurring target stimulus in a series of frequently occurring nontarget stimuli. ERPs recorded to frequently occurring nontarget stimuli elicit N1–P2 components, but no P3, whereas rare target stimuli elicit both N1–P2 and P3 components. The effects of alcohol on P3 will be discussed later in this section.

All studies examining the effects of alcohol on ERPs with the use of target-selection tasks report decrements in the amplitude of N1 to frequently occurring nontarget stimuli over central areas (Kopell *et al.*, 1978; Pfefferbaum *et al.*, 1980; Porjesz and Begleiter, unpublished; Rhodes *et al.*, 1975). Two visual ERP studies in the same laboratory (Obitz *et al.*, 1977; Rhodes *et al.*, 1975), using an identical target-selection paradigm but with different electrode configurations, confirm the findings with passive EPs that central but not occipital ERPs are depressed by alcohol. Marked amplitude reductions were reported at central leads, for all conditions, regardless of attentional factors (task versus no-task) (Rhodes *et al.*, 1975). Rhodes and his colleagues conclude that although both attention and alcohol significantly reduce ERP amplitude, the effect of attention is of a lesser magnitude than the effect of alcohol. Interestingly, when Obitz and co-workers (1977) introduced monetary reward, they were able to counteract alcohol-related slowed reaction times (RT) behaviorally; however, simultaneously recorded ERPs still manifested decreased N1 amplitudes, suggesting that alcohol-related ERP changes are independent of attentional factors (Rhodes *et al.*, 1975).

Although all target-selection paradigms report N1 decrements with alcohol (Kopell *et al.*, 1978; Pfefferbaum *et al.*, 1980; Porjesz and Begleiter, unpublished; Rhodes *et al.*, 1975), N1 decrements were not obtained by Roth *et al.*, (1977) using a memory retrieval paradigm. Roth *et al.*, postulate that the mobilization of attention under the memory retrieval conditions counteracted alcohol-produced N1 decrements. The discrepancy between results from target-selection and memory-retrieval designs can perhaps be explained in terms of differences in task requirements and complexity. Perhaps attention is mobilized to a greater extent under memory-retrieval conditions than under simple target-selection tasks. Roth and his colleagues do not report any significant RT differences between alcohol and placebo conditions, indicating that attention was indeed mobilized in their study.

Although target-selection studies have concluded that the effects of attention on ERP are not as influential as those of alcohol (Rhodes *et al.*, 1975), and memory-retrieval designs indicate that alcohol effects are not as strong as attentional effects (Roth *et al.*, 1977), these findings may not be as discrepant as they first appear. The net ERP result may represent an interaction between both factors and depend on the relative strength of each. Thus, it appears that the depressant effects of alcohol can be at least somewhat offset by attentional demands based on the complexity of task requirements. From the foregoing it can be concluded that the effects of alcohol on ERPs are not as simple as was first suspected but depend on a complex interaction of many factors, for example, dose of alcohol, time of testing, nutritional status, attentional factors.

P3. It is only very recently that the effects of acute alcohol ingestion on the P3 component have been investigated. A P3 or P300 component is a large, positive deflection that occurs approximately between 300–500 msecs after the stimulus. It can only be elicited under certain rather specific conditions related to the "subjective significance" of a stimulus. The subjective significance can be manipulated in a number of ways, namely: task relevance (Sutton *et al.*, 1967), unpredictability (Donchin *et al.*, 1978), infrequency (Tueting *et al.*, 1971) as well as by motivational factors (Begleiter *et al.*, 1983). The characteristics of P3 are unrelated to stimulus parameters and can even be elicited to the absence of an expected stimulus (e.g., emitted potentials). In terms of scalp topography, P3 has been found to be maximum over parietal areas; it is bilaterally distributed without apparent hemispheric asymmetry, with identical distributions regardless of the sensory modality of the stimulus (Simson *et al.*, 1976; 1977a; 1977b).

The effects of alcohol on P3 have been investigated with both visual (Porjesz and Begleiter, unpublished) and auditory (Campbell *et al.*, 1980; Kopell *et al.*, 1978; Neville *et al.*, 1981; Pfefferbaum *et al.*, 1980), target selection paradigms, and a visual Sternberg retrieval paradigm (Roth *et al.*, 1977). All of these P3 studies indicate a depression of P3 amplitude with alcohol; P3 latency delays were reported only for the target-selection paradigms. However, the condition under which P3 is attenuated varies depending on the task employed. A P3 component can be elicited to rare stimuli whether they are targets (designated signals to be attended, e.g., by counting) or nontargets (not designated to be specifically counted). All studies investigating P3 components to rarely occurring nontarget stimuli demonstrate significant P3 reduction with alcohol (Kopell *et al.*, 1978; Pfefferbaum *et al.*, 1980; Porjesz and Begleiter, unpublished). In fact, Kopell and co-workers report that P3 amplitude decreased so rapidly that it disappeared in many subjects. Of the studies examining P3 characteristics to target stimuli following alcohol ingestion, only Pfefferbaum *et al.*, (1980) do not report P3 amplitude decrements. P3 decrements to target stimuli following alcohol intake have been reported in both visual (Porjesz and Begleiter, unpublished) and auditory (Campbell *et al.*, 1980) target-selection designs as well as in a visual memory-retrieval paradigm (Roth *et al.*, 1977). However, recent studies may perhaps shed some light on these discrepant findings. Neville *et al.*, (1981) have reported that an individual's response to alcohol may result from his family history of alcohol abuse. They reported that while all subjects manifested increased P3 latencies following alcohol ingestion, only those with family histories of alcoholism additionally manifested decreased P3 amplitudes. P3 latencies have been reported to be significantly delayed following ethanol ingestion (Elmasian *et al.*, 1981; Neville *et al.*, 1981; Pfefferbaum *et al.*, 1980) to rare target stimuli in auditory target-selection paradigms, and slight but insignificant P3 latency delays were reported following ethanol ingestion in a similar auditory target-selection experiment (Campbell *et al.*, 1980). We have observed similar P3 latency increases following lg/kg alcohol in a visual target selection task (Porjesz and Begleiter, unpublished). Pfefferbaum *et al.* failed to report delays in P3 latencies to rare nontargets, and Neville *et al.* emphasize that it is only correctly identified targets that produce P3 delays. These results suggest that processing time may be slower when under the influence of alcohol when accurate task-relevant detection is required.

Thus, it seems that the effects of alcohol on normal brain functioning are not as straightforward as they first appeared. As different ERP tasks challenge the brain differently, the effects of alcohol are

superimposed on these more complex neurophysiological processes. Consequently, the nature of the task can drastically alter the results obtained and makes generalizing across different studies most difficult.

It is possible that other subject factors (besides family histories) remain to be identified to explain individual differences in response to alcohol. However, it seems apparent that, as with other drugs, individuals do not respond to alcohol in a homogeneous fashion, but rather display somewhat idiosyncratic modes of response.

Summary

The studies of acute doses of alcohol on evoked potentials in healthy volunteers, while differing in many methodological respects, concur that:

1. Acute alcohol ingestion prolongs central conduction times (Chu *et al.*, 1978; Fukui *et al.*, 1981; Squires *et al.*, 1978a, 1978b).
2. Subjects manifesting the flushing response to alcohol manifest greater BSP delays than "nonflushers" (Fukui *et al.*, 1981).
3. Alcohol depresses the amplitude of the EP late components (N1–P2) (Fukui *et al.*, 1981; Lewis *et al.*, 1969; Pfefferbaum *et al.*, 1977, 1980; Pfefferbaum, Roth, Tinklenberg, and Rosenbloom, 1979; Porjesz and Begleiter, 1975; Rhodes *et al.*, 1975; Salamy and Williams, 1973; Taghavy *et al.*, 1976).
4. Early components (<100 msec) are more resistant to the depressant effects of alcohol (Lewis *et al.*, 1970; Porjesz and Begleiter, 1975; Rhodes *et al.*, 1975) than late components.
5. Alcohol produces its maximal amplitude depression over association areas, as opposed to primary receiving areas (Porjesz and Begleiter, 1975; Salamy and Williams, 1973).
6. The rate of recovery of evoked potential amplitude is slower over association areas than over primary receiving areas (Porjesz and Begleiter, 1975).
7. There is an inverse relationship between the dose of alcohol, the blood alcohol level, and the evoked potential amplitude (Erwin and Linnoila, 1981; Salamy and Williams, 1973).
8. This EP amplitude depression primarily represents decreases in single EP amplitudes, rather than increased latency variability (Salamy, 1973).
9. Alcohol depresses right hemisphere responses in visual evoked potentials to a greater degree than left (Lewis *et al.*, 1969; Porjesz and Begleiter, 1975; Rhodes *et al.*, 1975).

10. Alcohol dissipates hemispheric asymmetry, where present prior to alcohol ingestion (Lewis *et al.*, 1969; Porjesz and Begleiter, 1975; Rhodes *et al.*, 1975).
11. The rate of recovery of evoked potential amplitude is identical over bilateral locations (Porjesz and Begleiter, 1975).
12. Acute alcohol administration reduces the slope of the A–I intensity gradient (Pfefferbaum *et al.*, 1977; Pfefferbaum, Roth, Tinklenberg, and Rosenbloom, 1979; Spilker and Callaway, 1969).
13. While most investigators report no change in latencies following acute alcohol ingestion (Gross *et al.*, 1966; Kopell *et al.*, 1978; Lewis *et al.*, 1970; McRandle and Goldstein, 1973; Rhodes *et al.*, 1975; Roth *et al.*, 1977) other investigators report increases in late component (N1–P2) latencies (Obitz *et al.*, 1977; Simpson *et al.*, 1981; Wolpaw and Penry, 1978).
14. The amplitude of the P3 component is reduced following acute alcohol ingestion (Campbell *et al.*, 1980; Kopell *et al.*, 1978; Porjesz and Begleiter, unpublished; Roth *et al.*, 1977) in some individuals (Neville *et al.*, 1981).
15. P3 latencies to target stimuli tend to be delayed following alcohol ingestion (Campbell *et al.*, 1980; Neville *et al.*, 1981; Pfefferbaum *et al.*, 1980; Porjesz and Begleiter, unpublished) in target selection but not memory retrieval tasks (Roth *et al.*, 1977).

These single dose studies are important in that they provide information about the direct effects of alcohol on normal brain functioning. This can be useful in determining the brain loci which are most affected by alcohol and the nature of brain functioning that is most susceptible to alcohol effects, perhaps providing a clue to the brain areas most affected by chronic alcohol abuse and the type of dysfunction (Porjesz and Begleiter, 1981c).

Chronic Alcohol Abuse

Although alcoholism is a uniquely human condition, it is very difficult to investigate systematically in man. Thus, although few studies have been undertaken in humans during chronic alcoholization (Begleiter *et al.*, 1973, 1974; Wagman *et al.*, 1978), the bulk of studies dealing with the various aspects of chronic alcohol administration on the EP have been performed in animals. The animal literature indicates that prolonged alcohol administration produces decrements in EP voltages (Bierley *et al.*, 1980) and delays in BSP latencies (Chu *et al.*, 1978); when tolerance develops, alcohol-related EP changes decrease

(Chu *et al.*, 1978). The abrupt removal of alcohol produces a rebound hyperexcitability, characterized by increased EP amplitudes (Begleiter and Porjesz, 1977, 1979; Bierley *et al.*, 1980; Hunter and Walker, 1980; Porjesz *et al.*, 1976) and significantly shortened BSPs (Chu *et al.*, 1978). This central nervous system (CNS) hyperexcitability has been found to persist after observable signs and symptoms of withdrawal have subsided (~3 weeks) (Begleiter and Porjesz, 1977, 1979; Begleiter, DeNoble, and Porjesz, 1980; Bierley *et al.*, 1980; Chu *et al.*, 1978; Porjesz *et al.*, 1976; Walker and Zornetzer, 1974). While brain damage and/or dysfunction can be detected with other techniques (e.g., CT-Scan, neuropsychological tests), at present only electrophysiological techniques (e.g., brain stem and evoked potentials) can discriminate between the various aspects of brain damage associated with alcoholism (intoxication, withdrawal, and long-term brain damage) (Begleiter and Porjesz, 1979; Zilm *et al.*, 1981). Because CNS hyperexcitability following alcohol intake can mask other forms of underlying brain damage, it is important to test alcoholics who are abstinent from alcohol for long periods of time after hyperexcitability has dissipated. Therefore, this section dealing with electrophysiological studies of chronic alcohol abuse will be divided into two separate subsections, those studies relating to CNS hyperexcitability (<3 weeks after withdrawal) and those relating to long-term brain dysfunction or damage and recovery (>3 weeks). However, this delineation is somewhat arbitrary and may not be clinically relevant.

Short-Term Abstinence (Withdrawal)

Auditory Brainstem Potentials (BSP). It has recently been reported that brain stem potential (BSP) latencies are sensitive indices of acute and chronic alcohol intoxication, alcohol withdrawal, and recovery in the rat (Chu *et al.*, 1978). As in their previous experiment, (Squires *et al.*, 1978a), acute intoxication resulted in delaying the central conduction time of peaks III–VII but additionally delayed peak II as well. Chronic intoxication for two weeks also resulted in peak and central conduction time slowing, but to a lesser extent, only affecting peaks V and VII. This suggests that tolerance to alcohol is also 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 prealcohol. When half of the rats ($n = 5$) were retested during a recovery period lasting up to 8 weeks after alcohol exposure, 4 of the 5 rats were found still to display slightly faster peak delays as late as 3–4 weeks postalcohol. By 8 weeks after withdrawal, all rats returned to normal peak latencies. Thus, it appears that underlying concomitants of withdrawal are still apparent long after acute symptoms of withdrawal

have subsided. We have observed similar persistence of later component amplitude increases following prolonged abstinence from chronic alcoholization (Begleiter, DeNoble, and Porjesz, 1980).

Evoked Potentials (EP). For the past several years in our laboratory, we have systematically studied the electrophysiological concomitants of withdrawal following the cessation of chronic alcohol intake in animals. We have demonstrated that alcohol withdrawal is accompanied by marked increases in evoked potential amplitudes in both rats and monkeys (Begleiter and Coltrera, 1975; Begleiter and Porjesz, 1977, 1979; Begleiter, DeNoble, and Porjesz, 1980; Porjesz *et al.*, 1976). We postulate that these enhanced amplitudes are the result of brain hyperexcitability. The persistence of these electrophysiological changes were found to be directly related to the length of alcohol exposure.

There is a paucity of studies that have examined human alcoholics during acute withdrawal (Begleiter *et al.*, 1973, 1974; Wagman *et al.*, 1978), perhaps because of the difficulties involved in testing. In one such study in our laboratory (Begleiter *et al.*, 1974), we examined recovery functions of somatosensory evoked potentials in chronic alcoholics during 4 days of intoxication and withdrawal, always recording 10 hours after the last drink (*i.e.*, the morning after). We found increased CNS excitability during withdrawal, and the degree of hyperexcitability increased with each additional day of alcohol intake. Thus, the results of our animal and human studies are in concordance with each other. These findings of increased amplitudes of cortical evoked potentials following alcohol withdrawal have been confirmed in human alcoholics abstinent at least 1 week by Coger *et al.*, (1976), Lelord *et al.* (1980), Porjesz and Begleiter (1979), and Wagman *et al.*, (1978).

Coger *et al.* (1976) found that alcoholics in withdrawal (1 week abstinent) manifested larger visual evoked potential (VEP) amplitudes (P100–N140) than normal controls. Furthermore, stabilized alcoholics (3–4 weeks abstinent) also exhibited higher VEPs than controls and did not differ significantly from the withdrawal group. Unfortunately, however, these results were contaminated by drug effects, as all alcoholics were taking Antabuse (disulfiram), which has subsequently been shown to increase EP amplitude (Peeke *et al.*, 1979). Thus, although it is possible that these increased VEP amplitudes are due to residual withdrawal and hence persisting CNS hyperexcitability, these results are not conclusive because of the Antabuse effects. Similar findings have also been obtained by Wagman *et al.* (1978), who examined VEPs in detoxified (7–21 days) chronic alcoholics during experimentally induced alcoholization and withdrawal. All alcoholics exhibited increased early component amplitudes (<130 msec), 16–17 days after

alcohol removal, particularly those alcoholics with low slow-wave-sleep (SWS). However, variable baseline measures were obtained anywhere between 7 and 21 days after detoxification, and were different for the low SWS ($\bar{X}$ 14 days) and normal SWS groups ($\bar{X}$ 24 days). Overresponsiveness has also been demonstrated by Lelord *et al.,* (1980), who reported that alcoholics abstinent from alcohol for 10 days were more responsive to phantom light than normal controls. The incidence of emitted potentials was higher in alcoholics than controls. Lelord *et al.* concluded that these findings indicate hyperexcitability in the alcoholic sample.

CNS excitability has also been investigated in chronic alcoholics using the augmenter–reducer continuum first studied by Petrie (1958, 1967) with the Kinesthetic Figural After-Effect (KFA). Petrie differentiated two types of individuals: augmenters, who tend to amplify responses to stimulation, and reducers, who tend to reduce responses to stimulation. Petrie observed that alcoholics tend to be augmenters and that alcohol ingestion reduces augmentation in augmenters. Buchsbaum (Buchsbaum and Pfefferbaum, 1971) demonstrated that cortical evoked potentials elicited by various light intensities could be used to distinguish between individuals who are augmenters and those who are reducers, with the use of an amplitude-intensity gradient (A-I slope). KFA augmenters exhibit an increasing VEP amplitude (P100–N140) with increasing stimulus intensities (positive slope), whereas reducers do not demonstrate this direct relationship (low or negative gradient) (Buchsbaum and Silverman, 1968). Petrie's hypothesis that alcohol ingestion decreases augmentation in augmenters has been confirmed with EPs in nonalcoholic augmenters (Pfefferbaum *et al.,* 1977; Pfefferbaum, Roth, Tinklenberg, and Rosenbloom, 1979; Spilker and Callaway, 1969), where decreased responses to higher intensities follow alcohol intake. Buchsbaum and Ludwig (1980) have recently confirmed Petrie's prediction of decreased augmentation following alcohol administration in alcoholics. Control subjects (reducers) in the same study reacted quite differently, by augmenting their responses following alcohol intake. Buchsbaum and Ludwig conclude that perhaps alcoholics depend on alcohol to inhibit their sensory input, since their A-I slope most resembled those of sober controls with the largest dose of alcohol (with reduced sensory stimulation at the highest intensities). Alcohol may in fact have a normalizing effect on the A-I slope, as has been suggested for many other physiological functions (Kissin, 1974; Reed, 1977), augmenting responses of reducers and reducing responses of augmenters.

The early observation by Petrie that alcoholics tend to be augmen-

ters has been supported by several evoked potential studies (Buchsbaum and Ludwig, 1980; Coger *et al.*, 1976; von Knorring, 1976; Ludwig *et al.*, 1977) particularly those with a family history of affective disorder (Martin *et al.*, 1979). This overresponsiveness (hyperexcitability) to high intensities may represent a lack of cortical inhibition in chronic alcoholics. Most of these studies reporting enhanced A-I gradients in abstinent alcoholics test them during the first two weeks of abstinence when withdrawal symptomatology has not yet subsided. Coger *et al.*, (1976) report that alcoholics in withdrawal (1 week) exhibited higher right-hemispheric A-I gradients than controls and stabilized (3–4 weeks abstinent) alcoholics. This suggests that as withdrawal diminishes, the A-I slope begins to return to normal. Furthermore, they reported a correlation between mean right-hemispheric VEP amplitude and A-I slope in alcoholics but not in normal controls. If one extrapolates from this relationship, it seems that the higher the VEP amplitude (or hyperexcitability), the higher the A-I slope (perhaps due to lack of cortical inhibition). Taken together, these studies all suggest that residual withdrawal phenomena (increased EP amplitudes) and A-I slopes persist in the human alcoholic and may last as long as 3 weeks after withdrawal. Our animal data indicate that the length of time this hyperexcitability lasts depends on the length of alcoholization. Abstinent animals that were challenged with a small dose of alcohol 2–5 weeks following withdrawal manifested increased evoked potential amplitudes (hyperexcitability), whereas naive control animals exhibited depressed evoked potentials at visual cortex. Evoked potentials of the two groups of animals were identical prior to the challenge dose. Animals that were alcoholized for 2 weeks manifested this latent hyperexcitability for a shorter time period than those alcoholized for 4 weeks; enhanced EPs to a challenge dose were exhibited as long as 5 weeks after withdrawal in animals alcoholized for 4 weeks.

Although enhanced cortical evoked potential amplitudes have been reported in abstinent alcoholics as late as 3 weeks after withdrawal (Coger *et al.*, 1976; Lelord *et al.*, 1979; Porjesz and Begleiter, 1979; Wagman *et al.*, 1978), the exact time-course of diminishing hyperexcitability has not been delineated. One reason for this problem is that different studies examine CNS reactivity at different arbitrary time points after alcohol abuse. The problem is further complicated when patients are tested at widely varying time points within the same study; for example, in Beck's laboratory, alcoholics are tested after anywhere between 13–93 days ($\overline{X} = 41$) of abstinence (Cannon, 1974; Dustman *et al.*, 1979). Thus, some alcoholics may be in a state of hypoexcitability and hence group data may be nonrepresentative. Although the exact

time-point at which EPs are recorded in abstinent alcoholics is critical in determining the level of CNS reactivity, it is not sufficient to ensure that they are in the same phase of recovery from alcohol. Alcoholics vary widely with respect to their drinking histories and susceptibility to alcohol-related CNS dysfunction, factors which affect the length of the protracted abstinence syndrome. In order to separate the persistent withdrawal concomitants from those of underlying long-term brain dysfunction or damage, it would be necessary to study longitudinally the time-course of CNS reactivity by recording EPs daily in the same individual.

Long-Term Abstinence

In contrast to the hyperexcitability (decreased latencies of BSPs and increased EP amplitudes) that may be apparent up to 3 weeks after withdrawal, studies examining electrophysiological disturbances in alcoholics abstinent for longer periods of time (>3 weeks) indicate that they manifest CNS hypoexcitability (increased BSP latencies and decreased EP amplitudes). There is a paucity of studies that have systematically examined long-term (>3 weeks) CNS disturbances in medication-free chronic alcoholics and their potential recovery. This has been undertaken in our laboratory for BSPs and ERPs (Begleiter and Porjesz, in preparation; Begleiter, Porjesz, and Tenner, 1980; Begleiter, Porjesz, and Chou, 1981; Porjesz and Begleiter, 1979, 1981a, b, 1982a; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980) and in Beck's laboratory for EPs (Cannon, 1974; Dustman *et al.*, 1979; Schenkenberg *et al.*, 1972).

Early Evoked Activity. In our laboratory we recently recorded auditory BSPs from alcoholics who were abstinent from alcohol for 1 month (Begleiter, Porjesz, and Chou, 1981). We found that alcoholic patients manifested delays in latencies and central conduction velocities of peaks II–V (Figure 1). These findings are remarkably similar to those reported by Squires *et al.* in animals (1978a) and man (1978b) with acute doses of alcohol. However, the delayed latencies manifested by intoxicated subjects in the Squires study were still within the normal range, whereas the chronic alcoholics in our investigation manifested delays well beyond the normal range (Figure 1). This study (Begleiter, Porjesz, and Chou, 1981) provides the first systematic electrophysiological evidence of brain dysfunction at levels other than the neocortex in chronic alcoholics, specifically with regard to increased neural transmission time in the brain stem. The increase in neural transmission time may reflect the process of demyelination, which has long been

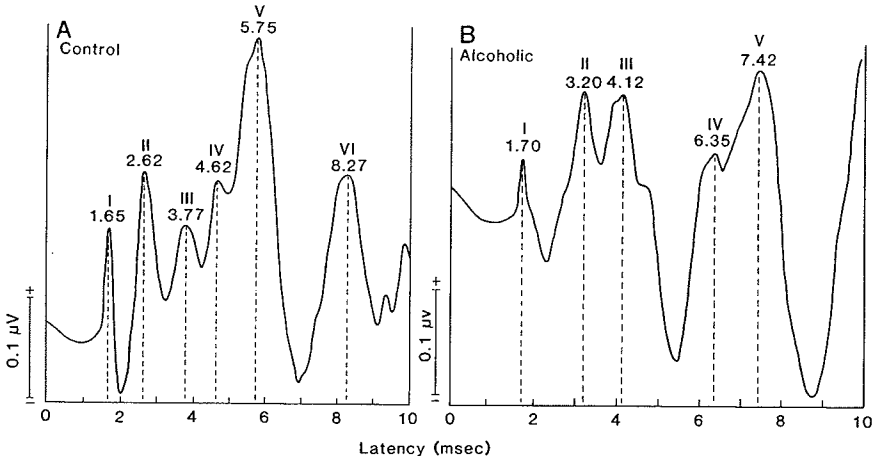

FIGURE 1. (A) Auditory brainstem potential (BSP) for one control subject indicating the latencies of peaks I to VI. (B) Auditory brainstem potential (BSP) for one alcoholic subject, with the latencies of peaks I to V indicated. Notice the delays in peaks II–V in the alcoholic subject when compared to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

suspected in chronic alcoholics (Adams *et al.,* 1959) and has been observed in rats chronically exposed to alcohol (Moscatelli and Demediuk, 1980). This study suggests that long-term alcohol abuse results in possible demyelination of auditory pathways beginning at the level of pontine formation. Similar results have been recently reported in neurologically impaired abstinent alcoholics (Chu and Squires, 1980). However, these increases in BSP latencies were not reported in rats following a single two-week chronic administration of alcohol (Chu *et al.,* 1978). During the early abstinence phase (acute withdrawal) these rats manifested earlier BSPs than those recorded prior to alcohol ingestion. Their recovery was marked by progressive increases of peak latencies, returning to prealcohol baseline levels. Perhaps only with repeated, prolonged exposures to alcohol do more permanent increases in central transmission time suggesting demyelination occur. Alcoholic patients in our study (Begleiter, Porjesz, and Chou, 1981) had been drinking for a minimum of 6 years and an average of 16 years. The drinking history factor(s) or interaction of factors (e.g., length of drinking history, amount consumed per sitting, number of withdrawals, severity of withdrawals, nutritional factors) that result in brain stem aberrations have not yet been determined; at present, we are investigating the relationship between these factors and magnitude of BSP aberration.

Another promising EP technique in the early diagnosis of demyelinating disorders in the visual system is the pattern-reversal or Pattern Evoked Potential (PEP) technique. This technique consists of the rapid presentation of alternating checkerboard patterns, such that the illuminated and nonilluminated areas reverse with successive presentations. This technique is very sensitive in assessing the integrity of the visual system (Halliday, 1978; Halliday *et al.*, 1973a, 1973b; Regan *et al.*, 1976) and can be used as an early diagnostic tool of neurological disorders such as multiple sclerosis, optic neuritis, and compression of the optic nerve (Halliday *et al.*, 1973a, 1973b, 1976; Hennerici *et al.*, 1977). We are currently examining chronic alcoholics abstinent for one month with the use of this technique (Begleiter, Porjesz, and Chou, in preparation).

We find that the characteristic positive component (P100) occurring at approximately 100 msecs in normal individuals is abnormally delayed in these chronic alcoholics. These results indicate an increase in transmission time in the visual sensory pathway that may represent demyelination of the optic pathways, the neurotoxic effects of alcohol on the retina, or deficits in the visual primary receiving area (occipital area 17). The exact nature of the deficit still remains to be clarified. Similar findings are currently being obtained in Holland by Posthuma and Visser (1982) and in Hungary by Janaky *et al.* (1980). These investigators report that 50 percent of their alcoholics are extremely impaired and that none manifest normal PEPs. The characteristics of the PEP that vary with check size, grid size, area of field, intensity, rate, and so forth have been carefully mapped by Regan (1972). In our study, we found that there is an inverse relationship between the number of squares per unit area and the latency of P100 in control but not alcoholic subjects. Therefore, it appears that chronic alcoholics manifest delayed latencies in early evoked potentials, suggestive of possible demyelination in both auditory and visual pathways. It is not certain at the present time whether these aberrations in sensory pathways recover with prolonged abstinence. The relationship between these early evoked potential measures and drinking histories remains to be determined.

Late Evoked Activity (ERPs)

There are very few studies that have examined brain dysfunction in long-term abstinent (>3 weeks) chronic alcoholics with the use of evoked potential (EP) or event-related-potential (ERP) techniques. Over the last decade, Beck and his colleagues have recorded VEPs in abstinent (<93 days) chronic alcoholics passively attending to repetitive flashes

(Beck *et al.*, 1978; Cannon, 1974; Dustman *et al.*, 1979; Schenkenberg *et al.*, 1972). More recently, investigators have applied ERP techniques, where the subject is actively engaged in a task, to study long-term brain dysfunction and possible recovery in abstinent chronic alcoholics. Target-selection paradigms have been used for both auditory (Pfefferbaum *et al.*, 1980; Pfefferbaum, Horvath, Roth, and Koppell, 1979; Salamy *et al.*, 1980) and visual (Begleiter, Porjesz, and Tenner, 1980, 1981; Porjesz and Begleiter, 1979, 1981a, b, 1982a; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980) sensory modalities. The major finding in most of these investigations is a decrease in late component amplitudes (N1–P2 and P3), and less pronounced, delayed late component latencies (hypoexcitability).

While most studies concur that the N1–P2 amplitude is diminished in long-term abstinent alcoholics, studies in which Antabuse (disulfiram) was administered for long periods of time do not report these late component amplitude depressions over association cortex (Cannon, 1974; Coger *et al.*, 1976; Salamy *et al.*, 1980). Recently, Peeke *et al.* (1980) have reported increases in ERPs with disulfiram in healthy volunteers. Contamination by medication is particularly critical when recovery or reversibility of brain deficits is being investigated. In the studies by Coger *et al.* (1976) and Salamy *et al.* (1980), increased amplitudes at 3–4 weeks may be due to the effects of withdrawal, the effects of Antabuse, interaction between detoxification and medication, or recovery from brain damage. It is difficult enough to attempt to separate withdrawal phenomena from those of more permanent underlying brain damage without further contamination from the effects of other medications.

For the past several years, we have systematically examined ERPs in abstinent chronic alcoholics who are medication-free. These ERP techniques require the subject to be engaged in a task, usually an information-processing task. Each task is designed to examine deficits in a particular ERP component. In one bimodal (visual and auditory) study (Porjesz and Begleiter, 1979), 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, a component that is sensitive to the selection of 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 irrelevant modalities (Hillyard *et al.*, 1973, 1978; Picton and Hillyard, 1974). A sequence of randomized flashes and clicks was 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 double clicks or ignoring all stimuli in an otherwise identical stimulus sequence. ERPs were obtained only to the irrelevant single flashes, which were either in the relevant or irrelevant stimulus modality in a given condition. The results indicated that abstinent alcoholics manifested abnormally reduced late component (N1–P2), but not early component amplitudes, particularly over right-hemisphere frontal and central association cortices. 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 obtained with acute doses of alcohol in healthy individuals (Lewis *et al.*, 1969; Porjesz and Begleiter, 1975; Rhodes *et al.*, 1975). This suggests that the brain dysfunction in chronic alcoholics resembles aberrations detected in normal persons under the influence of alcohol.

Similar findings of reduced late component amplitudes and the absence of hemispheric asymmetry over central areas in chronic alcoholics have been reported in Beck's laboratory with the use of passive VEPs (Schenkenberg *et al.*, 1972). In addition, our results confirm the findings in Beck's laboratory of delayed late component latencies (Cannon, 1974). Thus, the ERP results of our study (Porjesz and Begleiter, 1979) obtained while the subject was actively engaged in a task confirm previous findings with repetitive flashes in abstinent alcoholics (Schenkenberg *et al.*, 1972; Cannon, 1974).

The advantage of using an information-processing ERP design to assess brain functioning is that it provides information comparing responses to identical relevant and irrelevant inputs, not possible with passive EP techniques. Consistent with the ERP literature (Hillyard *et al.*, 1973; 1978), control subjects in our study (Porjesz and Begleiter, 1979) manifested significantly enhanced N1 components over association areas to stimuli in the relevant as opposed to the irrelevant modality, while alcoholics maintained the same low amplitude of N1 regardless of degree of task relevance. This suggests that chronic alcoholics are incapable of appropriate sensory filtering since they do not differentiate electrophysiologically between relevant and irrelevant channels.

In another study in our laboratory, we investigated brain dysfunction in chronic alcoholics with the P3 or P300 component in a target-selection visual ERP paradigm (Porjesz, Begleiter, and Garozzo, 1980). We were interested both in the ability of chronic alcoholics to differentiate between relevant and irrelevant inputs and in their ability to probability-match stimuli in terms of their frequency of occurrence. The experimental design required them to change sets; stimuli that

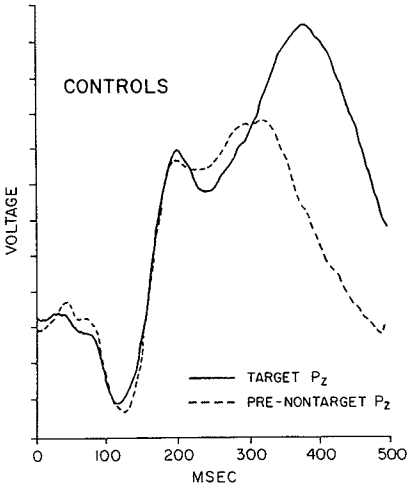

FIGURE 2. Grand mean ERP waveforms recorded at parietal electrode (Pz) to the target stimulus (solid line) and nontarget stimulus (dashed line) in healthy subjects. Notice the prominent P3 component (large positive deflection occurring between 300–450 msec) to the target stimulus.

were relevant in one block were no longer relevant in another block, but all stimuli were in the relevant modality (and hence would be expected to have enhanced N1 components). ERPs were obtained to targets (rarely occurring, task-relevant geometric shapes), nontargets (frequently occurring, task-irrelevant geometric shapes), and novel stimuli (rarely occurring, task-irrelevant random shapes). The subject's task was to press a button only to the target stimulus. Target and nontarget stimuli were alternated every other block so that ERPs could be obtained to the same stimulus when it served as a target or nontarget.

As in our bimodal experiment (Porjesz and Begleiter, 1979), we found that the late component amplitude N1–P2 was significantly depressed in alcoholics to all stimuli (target, nontarget, and novel), to levels comparable to an irrelevant stimulus modality, despite the fact that all stimuli were in the relevant modality. Taken together, these studies suggest that sensory-filtering mechanisms are impaired in chronic alcoholics.

Furthermore, we found that P3 amplitudes were significantly depressed or absent in alcoholic patients to rare target stimuli under conditions optimal for eliciting large P3s (Donchin *et al.*, 1978). This finding was most pronounced over parietal areas, where P3 amplitude is maximal at scalp (Ritter *et al.*, 1968; Simson *et al.*, 1977a; 1977b). 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, whereas normal controls manifested differentially enhanced, late P3 components to target stimuli (Figure 2), alcoholics manifested 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 ERP aberration manifested by chronic alcoholics is the lack of differentiation between their responses to relevant and irrelevant inputs and the low voltages of their event-related activity. This seems to suggest underlying brain dysfunction that impairs sensory filtering and probability-matching processes.

The P300 component of the ERP has been considered to be a manifestation of the orienting response (Donchin, 1979, 1981; Ritter *et al.*, 1968; Roth, 1973). Certain non-modality-specific hippocampal neurons are reported to be involved in the orienting response (Vinogradova, 1970). These neurons compare incoming stimuli, reacting to significant or novel stimuli and inhibiting responses to repeated stimuli during habituation. Despite its maximal amplitude over parietal areas at the scalp, the neural origins of P300 are not presently known. Recent evidence suggests that its origins may be subcortical and implicates the amygdala and hippocampus. One recent study investigating the neural origin of P3 with implanted electrodes in humans reported that P300 was maximum at subcortical loci (Wood *et al.*, 1979). Similarly, Halgren

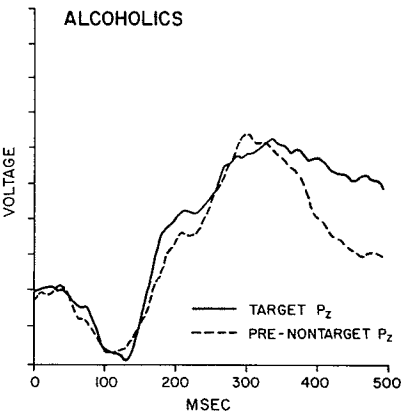

FIGURE 3. Grand mean ERP waveforms recorded at parietal (Pz) to the target (solid line) and nontarget (dashed line) stimuli in the alcoholic group. Compare the P3 component of the target stimulus to that of the control group (Figure 2), and notice how reduced it is in amplitude. Also notice the lack of difference between P3 amplitudes to target and nontarget stimuli in the alcoholic group in this figure.

et al. (1980) have just completed a study with implanted electrodes in humans in which they recorded large late potentials from limbic system. They postulate that the P3 may be generated in the hippocampus or amygdala.

Thus, our results that chronic alcoholics manifest low-voltage or even absent P300 components under conditions designed to elicit maximum P3 amplitudes may be indicative of hippocampal deficits. Although these results do not rule out the contributions of cortical sites, they emphasize the important role of limbic structures in generating the P300 component. The involvement of the hippocampus in chronic alcohol intake in the absence of malnutrition has been recently demonstrated in neuropathological (Riley and Walker, 1978; Walker *et al.*, 1980, 1981) and electrophysiological (Begleiter, DeNoble, and Porjesz, 1980) studies with animals. Long-term ethanol consumption has been found to result in the loss of dendritic spines in mouse (Riley and Walker, 1978) and rat (Walker *et al.*, 1980) hippocampus. In our laboratory, we have also demonstrated a susceptibility to both acute and chronic alcohol effects on evoked potentials recorded from monkey hippocampus (Begleiter, DeNoble, and Porjesz, 1980). Thus, our results with P300 suggest the possible involvement of hippocampal deficits in chronic alcoholics.

We have recently become interested in determining the relationship between electrophysiological deficits and cortical atrophy observed in chronic alcoholics (Begleiter, Porjesz, and Tenner, 1980). We selected two groups of alcoholics who had been subjected to CT-Scans following one month of abstinence: namely, those manifesting a high degree of cortical atrophy (Pos-CT) and those without any evidence of cortical atrophy (Neg-CT). Patients in the two groups did not differ with regard to age, education, or drinking history (duration and amount). ERPs were recorded on the same day as the CT-Scan and involved the same P3 paradigm previously described (Porjesz, Begleiter, and Garozzo, 1980).

We found that both groups of alcoholic patients manifested lower P3 amplitudes to target stimuli than did normal controls. This replicates our previous finding with chronic alcoholics not differentiated in terms of CT-Scan (Porjesz, Begleiter, and Garozzo, 1980). Alcoholics with enlarged cortical sulci (Pos-CT) had significantly lower (or absent) P3s to target stimuli than did alcoholics without signs of cortical atrophy (Neg-CT). Again, in agreement with our previous results, we found that both groups of alcoholics displayed similar P3 components to all categories of stimuli, regardless of task relevance.

These findings suggest that, in man, chronic alcohol abuse not only results in atrophic changes in the cortex but may also involve electrophysiological aberrations indicative of subcortical (e.g., hippocampal) deficits. Often the cortical deficits in chronic alcoholics are emphasized while subcortical aberrations are overlooked, perhaps because the techniques currently employed (e.g., CT-Scan) can more readily detect cortical atrophy than sucortical aberrations. While cortical atrophy can be readily observed on a CT-Scan, subcortical change may not be easily apparent.

We have recently completed a study examining the N2 or N200 component of the ERP in abstinent alcoholics (Porjesz and Begleiter, 1981a, 1981b). The N200 component is a modality-specific negative deflection with a maximum amplitude at occipito-parietal scalp for the visual modality and at central regions for the auditory modality. Recent evidence suggests that the latency of N2 can be taken as an early index of stimulus evaluation time (Renault and Lesevre, 1979), being longer for more difficult discriminations (Gaillard and Lawson, 1980; Ritter *et al.*, 1979; Towey *et al.*, 1980). The N200 component is a better index of stimulus evaluation time than the reaction-time (RT) because it is not confounded by the motor response. The reaction time is a complex measure of speed of information-processing since it depends on the end product of stimulus evaluation, response selection and organization, and the motor response. Therefore, although there are some reports of delayed RTs in chronic alcoholics (Bertera and Parsons, 1973; Talland, 1963; Vivian *et al.*, 1973) these studies cannot determine which aspect of information processing is slower in alcoholics. We were interested in specifically examining the speed of stimulus evaluation in chronic alcoholics, using the N2 component of the ERP. Therefore, we designed a RT study involving easy and difficult line orientation discriminations. This visual-spatial RT design enabled us to investigate the relationship between difficulty of discrimination, N2 latency, P3 characteristics, and RT in abstinent chronic alcoholics. ERPs were obtained to frequent nontargets (vertical line) and occasional easy (90-degree deviant from vertical) and difficult (3-degree deviant) line orientations.

Our results indicated that the latency of N2 reflected difficulty of discrimination in the control subjects, being significantly delayed to the difficult when compared to the easy discrimination; in the alcoholics, however, there was no difference in N2 latency depending on difficulty of discrimination. Furthermore, the N2 latency occurred significantly later in the alcoholic group than in the control group for both easy and

difficult discriminations, suggesting that alcoholics find the discrimination task more difficult and hence need more time for stimulus evaluation. The latency difference between groups was even more apparent for the easy discrimination than for the difficult discrimination. This suggests that alcoholics need disproportionately more time to make an easy discrimination (vertical from horizontal) when compared to controls (who can process this information more quickly), than to make a difficult discrimination (which both groups presumably find difficult). In addition, alcoholics manifested delayed P3 latencies to easy discriminations when compared to controls; these P3 latencies were comparable to those expected for a difficult task. These results suggest that alcoholics adopt an undifferentiated mode of responding regardless of task requirements, finding all tasks difficult. While the amplitude of N2 was larger for easy discriminations than difficult discriminations in the control group, the amplitude of N2 was the same in the alcoholics regardless of task difficulty. The amplitude of N2 has been shown to be directly related to degree of stimulus deviance in normal subjects (Naatanen, 1981). There were no significant differences in RTs between the two groups of subjects, although the alcoholics tended to have somewhat faster RTs than controls. However, the alcoholics tended to make more errors, both in terms of false alarms and missing target stimuli, although these results were not significant. This response pattern suggests that alcoholics adopt response strategies different from those of controls, stressing speed over accuracy (Kutas *et al.*, 1977). This perhaps implies a lack of inhibition in chronic alcoholics reflected by their apparent inability to withhold responding until certainty of accuracy or correctness has been established.

In addition to these latency results, we once again confirmed our previous findings (Begleiter, Porjesz, and Tenner, 1980; Porjesz and Begleiter, 1982a; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980) that alcoholics have significantly depressed P3 amplitudes; this was even more apparent for the easy discrimination, where controls exhibited very high P3 voltages. In the control group but not in the alcoholic group, the baseline-P3 voltage was significantly higher for the 90-degree target when compared to the 3-degree target. This result is predicted by many ERP studies that have demonstrated that the more deviant a rare stimulus is from the background (the more easily discriminable it is), the larger the P3 amplitude (Ford *et al.*, 1979; Johnson and Donchin, 1978; Ritter *et al.*, 1972; Ruchkin and Sutton, 1978; Towey *et al.*, 1980). Perhaps the lack of P3 amplitude difference in the alcoholic group indicates that they are more uncertain of the correctness of their decision than are controls since they stress speed

over accuracy. Furthermore, whereas controls manifest significant target/nontarget baseline-peak P3 measures, alcoholics do not. Thus, on the basis of both the N2 and P3 ERP components, it was concluded that alcoholics have difficulty evaluating the potential significance of a stimulus. They do not differentiate electrophysiologically between relevant and irrelevant, or easy and difficult discriminations but rather maintain the same ERP characteristics (both amplitude and latency), regardless of the task requirements. This perhaps indicates that their template for match/mismatch decisions is lost or not readily available. In either case, this suggests a memory deficit requiring that each incoming stimulus be evaluated anew. Our data suggest that alcoholics manifest both types of brain dysfunction; the delay in N2 latency suggests that the template for comparison is not as easily accessible in the alcoholic, and the low P3 voltages suggest that, once retrieved, the match/mismatch processes themselves are impaired in chronic alcoholics.

Thus, taken together our ERP studies with long-term (>3 weeks) abstinent chronic alcoholics concur that alcoholics manifest low voltages. They exhibit depressed N1–P2 amplitudes to all stimuli, regardless of whether they are in the relevant or irrelevant information-processing channel (e.g., stimulus modality) (Porjesz and Begleiter, 1979; Porjesz, Begleiter, and Garozzo, 1980), suggesting sensory filtering deficits. Furthermore, they manifest depressed or absent P3 components to task-relevant target stimuli (Begleiter, Porjesz, and Tenner, 1980; Begleiter, Porjesz, Chou, and Aunon, in preparation; Porjesz and Begleiter, 1981a, b; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980). Alcoholics do not exhibit differentially enhanced P3 amplitudes depending on the relevance or unpredictability of a stimulus (Begleiter, Porjesz, and Tenner, 1980; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980), regardless of whether or not they manifest cortical atrophy (Begleiter, Porjesz, and Tenner, 1980). Although all alcoholics manifest depressed P3 amplitudes to target stimuli, those with cortical atrophy manifest even lower voltages of P3 activity (Begleiter, Porjesz, and Tenner, 1980, 1981). Similarly, alcoholics manifest the same low amplitudes of N2 and P3, regardless of the deviance of the stimulus from the background (Porjesz and Begleiter, 1981a, 1981b). They manifest delayed N2 latencies to both easy and difficult discriminations when compared to controls (Porjesz and Begleiter, 1981a, 1981b) and do not manifest differentially early N2 latencies to easy discriminations; they manifest additionally delayed P3 latencies to easy discriminations only (Porjesz and Begleiter, 1981b). Thus, on the basis of our studies it appears that alcoholics tend to manifest the same ERP characteristics (amplitude and

latency) regardless of the task requirements (Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980; Begleiter, Porjesz, and Tenner, 1980; Porjesz and Begleiter, 1981a, 1981b). This suggests that match/mismatch processes are deficient in chronic alcoholics, implying that memory processes are impaired.

Despite the consistency of results across studies in our laboratory with regard to N1 and P3 amplitude decrements in chronic alcoholics, Pfefferbaum *et al.* (1980; Pfefferbaum, Horvath, Roth, and Kopell, 1979) have obtained different findings using an auditory reaction-time target-selection task. In contrast to our findings, their results indicated no difference between N1–P2 or P3 amplitudes between alcoholic and controls for any stimuli (rare targets and nontargets and frequent nontargets). P3 latencies were delayed to all rare stimuli (whether target or nontarget), while the latency of N1 and P2 were not significantly different between groups. Behaviorally, the alcoholic and control groups did not differ from each other in terms of number and type of errors and reaction time (RT). Pfefferbaum and colleagues note that the ERP pattern of delayed P3 without delays in latencies of N1 and P2 is similar to that reported by Goodin, Squires, and Starr (1978) for a variety of dementias, and they therefore conclude that ERPs of chronic alcoholics resemble those seen in demented patients. However, Goodin and his associates demonstrated this ERP pattern only for demented patients, regardless of the etiology of dementia; patients with the same medical diagnosis (e.g., hydrocephalus, cerebrovascular disease, or even alcoholism), but without evidence of dementia, did not display this ERP pattern. The alcoholic sample Pferrerbaum *et al.* (1980) examined were clearly not demented; in fact, on the Halstead–Reitan Test, only 3 out of 10 alcoholics had scores that were below normal. Furthermore, the demented patients in the Goodin, Squires, and Starr (1978) study showed a concomitant decrease in amplitude of P3, in conjunction with P3 latency shifts not shown by nondemented patients. Pfefferbaum *et al.* (1980) did not observe P3 amplitude decrements in their chronic alcoholics and in fact report a slight, although insignificant P3 amplitude increase. Therefore, the ERP pattern observed in chronic alcoholics by Pfefferbaum and co-workers is quite different from that reported for dementia.

The ERP findings of Pfefferbaum *et al.* (1980) in chronic alcoholics differ from those reported in other laboratories, including our own. Although they fail to report N1–P2 amplitude decrements and delayed latencies in long-term abstinent chronic alcoholics who are medication free, this has been reported for both auditory (Salamy *et al.*, 1980) and visual stimuli (Cannon, 1974; Dustman *et al.*, 1979; Porjesz and Begleiter,

1979; Porjesz, Begleiter, and Garozzo, 1980; Schenkenberg *et al.*, 1972). There are fewer data available about P3 deficits in chronic alcoholics, perhaps because it requires a special experimental paradigm. Although the experimental design of Salamy *et al.* (1980) is a P3 paradigm, inexplicably they only discuss the results they obtained with N1–P2 in chronic alcoholics. Thus, the only two laboratories reporting P3 aberrations in chronic alcoholics report discrepant results. We have recently confirmed our findings of P3 amplitude decrements in chronic alcoholics under various different experimental paradigms (Begleiter, Porjesz, Chou, and Aunon, in preparation; Porjesz and Begleiter, 1981a, 1981b).

It is unclear at the present time why the results from our laboratory differ from those of Pfefferbaum *et al.* (1980). However, there are numerous methodological differences that may account for the discrepancy in findings. The studies differ in terms of patient populations used with respect to age, sex, neuropsychological deficits, and length of abstinence from alcohol. All of these factors produce differences in ERPs. The group of alcoholics investigated by Porjesz *et al.*, (1980a, 1980b) had a mean age of 36; those examined by Pfefferbaum *et al.*, (1980) had a mean age of 50.1. Since the ERP is very sensitive to the effects of aging (Ford *et al.*, 1979; Goodin, Squires, Henderson, and Starr, 1978; Porjesz and Begleiter, 1982a, 1982b; Porjesz, Begleiter, and Samuelly, 1980), these effects may have interacted with alcohol effects, perhaps explaining the difference in results. There is evidence in the neuropsychological literature that alcohol abuse is more likely to cause brain dysfunction in an old alcoholic than a young alcoholic. In terms of neuropsychological assessment, our patients seem to be more deterioriated than those of Pfefferbaum *et al.* (1980). For example, 60 percent of our patients were impaired on the Digit–Symbol test, and at least 40 percent were impaired on Symbol–Digit, Trail-Making (A + B), and Benton Visual Retention tests. Furthermore, our subjects tend to be unemployed, recurrent alcoholics with unstable or nonexistent family lives, while those of Pfefferbaum *et al.* (1980) are socially intact patients in the VA system. However, it is possible that genetic differences may account for our discrepant results. The majority of alcoholics within our sample have family histories of alcoholism, but those of Pfefferbaum (1981, personal communication) may not. Since it has been demonstrated by Neville *et al.* (1981) that a family history of alcoholism determines an individual's responsiveness to alcohol (decreases in P3 amplitude were reported only for individuals with a family history of alcoholism), it is possible that the differences in P3 results between our laboratory and that of Pfefferbaum are due to this difference in genetics.

We are currently comparing our P3 data obtained from alcoholics with family histories of alcoholism with those of our alcoholics without family histories of alcoholism.

Furthermore, length of abstinence has been demonstrated to have drastic effects on the ERP (Begleiter and Porjesz, in preparation; Coger *et al.*, 1976; Salamy *et al.*, 1980). Whereas Pfefferbaum's patients were abstinent a minimum of 2 weeks and an average of 21 days, our patients were abstinent a minimum of 3 weeks in all our studies and an average of 2 months in analogous visual target-selection paradigms (Begleiter *et al.*, 1980a,b; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980). In more recent studies, we have replicated our previous P3 findings in alcoholics who were abstinent for 26–30 days (~1 month).

In addition to differences in patient populations, there are differences in measurement techniques and experimental designs. In terms of measurement of the ERP, Pfefferbaum *et al.* (1980) use Woody filtering, wherein ERPs are averaged on the basis of latency-corrected peaks. We are currently using these procedures to determine whether our P3 amplitude results will change with these procedures. In addition, there are many differences in experimental design. The target-selection study by Pfefferbaum *et al.* (1980) is auditory while ours is visual (Begleiter, Porjesz, and Tenner, 1980; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980). Furthermore, the type of task is different in the two studies; Pfefferbaum *et al.* (1980) stressed speed of responding by using a reaction-time task, whereas speed was not a factor in our analogous study, as it was not a RT task. It has been found that P3 characteristics are very different depending on whether speed or accuracy is stressed (Kutas *et al.*, 1977). These investigators found that P3 latency correlates with speed of RT response when accuracy but not speed of response is stressed. It should be noted that we recently used a RT task and did in fact obtain P3 latency delays in abstinent alcoholics, but only to easy and not difficult discriminations (Porjesz and Begleiter, 1981b). This suggests that task difficulty may be a factor in accounting for differences between our earlier visual target-selection paradigm with geometric shapes (Begleiter *et al.*, 1980a; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980) and Pfefferbaum's (Pfefferbaum *et al.*, 1980) auditory tone discrimination target selection design. This tone discrimination task is considerably easier than our visual shape discrimination task, particularly as we alternated targets and nontargets in this design. Therefore, it appears that when tasks are sufficiently easy, control subjects are

capable of electrophysiologically processing information faster, whereas alcoholics respond as though all tasks were difficult. It should be noted that in our RT study varying difficulty of discrimination of target stimuli, both N2 and P3 component latencies were significantly earlier to easy discriminations in controls than in alcoholics. Although most attention relating RT and ERP components have focused on the P3 component, P3 often occurs after the motor response has been made. Insofar as stimulus evaluation time correlates with RT, the earlier N2 component correlates with RT (Renault and Lesevre, 1979; Ritter *et al.*, 1979). Recent evidence suggests that N2 may be a better index of stimulus evaluation time than P3 and that increases in P3 with task difficulty are in fact secondary to N2 increases with task difficulty (Ritter *et al.*, 1979; Towey *et al.*, 1980).

Thus, the differences in results between our laboratory and that of Pfefferbaum are not as discrepant as they first appeared. While latency results can perhaps be explained in terms of experimental variables such as task difficulty, amplitude differences may in fact be due to inherent differences in patient populations. 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 tapping underlying functional brain deficits than had been previously assumed. ERP components are extremely sensitive to rather specific and often subtle factors, but they 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 becomes definitively elucidated, this ERP complexity will prove to be an advantage rather than a drawback in delineating specific aspects of brain functioning and dysfunctioning in chronic alcoholics.

Reversibility

The issue of reversibility of electrophysiological brain abberations has not received a great deal of attention in the evoked potential literature. At present, it is most difficult to assess the few studies that have attempted to deal with this issue since they really test "detoxified" rather than "recovered" alcoholics. As the various electrophysiological measures (EP, BSP) are particularly sensitive to withdrawal phenomena (increased EP amplitudes and shortened BSP latencies), and these electrophysiological changes are known to persist for long periods of

time far outlasting overt withdrawal symptomatology (Begleiter and Porjesz, 1977, Porjesz *et al.*, 1976), so-called reversibility may in fact merely represent the subsiding of withdrawal concomitants. On the other hand, changes in evoked potentials with abstinence may indicate recovery from other forms of brain damage. In addition to the problems of residual withdrawal symptomatology masking other forms of underlying brain damage is the problem of the use of medication. Both published evoked-potential studies comparing alcoholics at different time points after withdrawal (Coger *et al.*, 1976; Salamy *et al.*, 1980) administered Antabuse to the subjects. In fact, Coger *et al.* report higher amplitudes in patients receiving Antabuse when compared to the other patients. More recently, Peeke *et al.* (1980) have reported increased ERPs with disulfiram in healthy volunteers. Both of these studies examined alcoholics initially at 1 week after withdrawal and at 3–4 weeks (Coger *et al.*, 1976) or 4 weeks (Salamy *et al.*, 1980). This is much too short a time span to examine recovery from brain damage and at best can delineate the diminishing of underlying withdrawal. However, despite these similarities in post-withdrawal testing periods, the results of the two studies are quite different. Coger *et al.* (1976) found that at both 1 week and 3–4 weeks after withdrawal alcoholics manifested higher amplitudes than controls. There was no significant difference between amplitudes at 1 week and 3–4 weeks. However, it should be noted that this was a cross-sectional study with different subjects in the 1 week and 3–4 week groups. Therefore, this study does not unequivocally address the issue of reversibility.

In direct contrast to these findings, Salamy *et al.* (1980) reported that N1–P2 amplitudes recorded during auditory target-selection tasks were significantly lower at 1 week at all leads (F3, F4, P3, P4). Following three additional weeks of abstinence in the same patients, these amplitudes were found to recover at parietal but not frontal leads. Unfortunately, during the first week of abstinence, prior to testing, patients were administered chlordiazepoxide (Librium) for 4 days and thereafter were placed on disulfiram (Antabuse). Thus, at the time of the first test they had just changed medications, and hence the interactive effects of detoxification from alcohol, chlordiazepoxide, and disulfiram could have contributed to the apparent recovery phenomenon; at the time of retesting they had been taking disulfiram for over 3 weeks. This is the same problem previously discussed with regard to the data of Cannon (1974) and Coger *et al.* (1976). In all three of these studies, late component amplitude depressions were not reported while the subjects were on Antabuse for long periods. Therefore, it is difficult to ascertain whether the changes in amplitude over time are due to the effects of

subsiding withdrawal, an interaction between detoxification and medication, or recovery of brain damage in all of these studies. It is difficult enough to attempt to separate withdrawal phenomena from those of more permanent underlying brain damage without further contamination with the effects of other medications. However, despite the difficulties with this study, it is an interesting attempt at ascertaining possible recovery from toxic effects of alcohol with long-term abstinence in chronic alcoholics.

In our own laboratory, we have undertaken a program of examining the reversibility of EP and ERP deficits observed at 1 month and 3 months of abstinence from alcohol in chronic alcoholics. It should be noted that our time point of initial testing (1 month) is the final ("recovered") test time in the aforementioned studies. Preliminary group data suggest some improvement in all measures, although they do not approach comparable normal scores. Some decreases in latencies and delayed conduction time were noted in BSP and PEP measures, as well as improved morphology of waveforms; however, neural transmission velocities still remained slower than those of control subjects following 4 months of abstinence. Some improvement in ERP morphology was also apparent, with improved signal/noise ratios with prolonged abstinence. However, although some alcoholics manifested overall enhancements of N1–P2 and P3 components from initial testing, most alcoholics did not. Furthermore, an interesting finding was that there was no change in differential enhancement of N1 and P3 amplitudes on the basis of task-relevance even in those alcoholics manifesting general improvement in ERPs. But a cursory look at these data subdivided according to age indicates that more reversibility occurs in younger alcoholics than older alcoholics with comparable drinking histories. Reversibility is most apparent in amplitudes of late components in younger alcoholics who did not manifest BSP delays at initial testing. Some young alcoholics seem to be more resistant to electrophysiological aberrations at initial testing, and this special sample of alcoholics manifested the most reversibility. Another factor that seemed to play a role in reversibility was family history of alcoholism. When alcoholics were divided according to whether there was a history of alcoholism in their family, those with family histories of alcoholism showed the least improvement. However, they were also more impaired at initial testing. Unfortunately, alcoholics with positive family histories of alcoholism in our sample also tended to have more severe drinking histories and tended to be somewhat older. Furthermore, they were less likely to remain in treatment for the four months of abstinence required. Perhaps then, the sample in which we are able to test reversibility is less

impaired in the first place and is not representative of our alcoholic population in general. At present, as these are preliminary data based on small sample sizes, caution is suggested in interpreting the results. We are currently continuing to examine this issue with increasing sample sizes in an effort to determine the important factors in both susceptibility and reversibility of brain dysfunction in alcoholism.

Summary

Although at present it is somewhat premature to draw unequivocal conclusions about the nature of evoked potential changes related to chronic alcoholism, the following tentative conclusions can be drawn:

1. Chronic alcohol administration results in decrements in EP voltages (Bierley *et al.*, 1980; Zilm *et al.*, 1981) and delays in BSP latencies (Chu *et al.*, 1978).
2. With the development of tolerance, alcohol-related EP changes decrease (Porjesz *et al.*, 1976; Zilm *et al.*, 1981), as do BSP delays (Chu *et al.*, 1978).
3. The abrupt removal of chronic alcohol administration elicits increased EP amplitudes (Begleiter and Coltrera, 1975; Begleiter and Porjesz, 1977, 1979; Begleiter *et al.*, 1974; Bierley *et al.*, 1980; Hunter and Walker, 1980; Porjesz *et al.*, 1976; Zilm *et al.*, 1981) and significantly shortened BSPs (Chu *et al.*, 1978), characteristic of CNS hyperexcitability.
4. This CNS hyperexcitability persists for long periods of time (> 3 weeks), far beyond observable signs and symptoms of withdrawal have subsided (Begleiter and Porjesz, 1977, 1979; Begleiter, DeNoble, and Porjesz, 1980; Bierley *et al.*, 1980; Chu *et al.*, 1978; Porjesz *et al.*, 1976; Walker and Zornetzer, 1974).
5. Short-term abstinent alcoholics manifest enhanced early component amplitudes (Coger *et al.*, 1976; Lelord *et al.*, 1980; Porjesz and Begleiter, 1979; Wagman *et al.*, 1978), particularly to higher intensities of stimulation, to which they overrespond, that is, they tend to be augmenters (Buchsbaum and Ludwig, 1980; Coger *et al.*, 1976; Ludwig *et al.*, 1977; Martin *et al.*, 1979). These results suggest latent hyperexcitability in abstinent alcoholics (Porjesz and Begleiter, 1981c).
6. Long-term abstinent alcoholics manifest delayed transmission times in auditory BSP (Begleiter, Porjesz, and Chou, 1981; Chu and Squires, 1980) and visual pattern reversal EPs (Begleiter, Porjesz, and Chou, in preparation; Janaky *et al.*, 1980;

Posthuma and Visser, 1982) suggestive of demyelination of sensory pathways.

7. Long-term abstinent (>3 weeks) alcoholics display lower voltage N1–P2 amplitudes (Begleiter, Porjesz, and Tenner, 1980; Cannon, 1974; Dustman *et al.*, 1979; Porjesz and Begleiter, 1979, 1980a, 1980b; Schenkenberg *et al.*, 1972), and delayed N1–P2 latencies (Cannon, 1974; Dustman *et al.*, 1979; Porjesz and Begleiter, 1979; Salamy *et al.*, 1980; Schenkenberg *et al.*, 1972) to all stimuli, regardless of whether they are in the relevant channel (Begleiter *et al.*, 1980a; Porjesz and Begleiter, 1979; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980; Salamy *et al.*, 1980). This suggests that sensory-filtering processes are impaired in chronic alcoholics (Porjesz and Begleiter, 1981c).
8. Long-term abstinent alcoholics (1 month) manifest absent or reduced P3 amplitudes to task-relevant visual target stimuli (Begleiter, Porjesz, and Tenner, 1980; Begleiter, Porjesz, Chou, and Aunon, in preparation; Porjesz and Begleiter, 1981a, 1981b, 1982, in preparation; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980) when compared to healthy nonalcoholic controls; however, those with cortical atrophy on CT-Scan manifest even lower P3 voltages than those without cortical atrophy (Begleiter *et al.*, 1980a; Begleiter, Porjesz, and Tenner, 1981). This implies that probability-matching (match/mismatch) processes themselves are deficient in chronic alcoholics, suggesting hippocampal and amygdala damage (Porjesz and Begleiter, 1981c).
9. Alcoholics manifest delays in processing time when compared to controls (Pfefferbaum *et al.*, 1980; Porjesz and Begleiter, 1981b), particularly for easy discriminations (Porjesz and Begleiter, 1981a, 1981b). Alcoholics manifest increased N2 latencies to target stimuli, (Porjesz and Begleiter, 1981a, 1981b), and P3 latency delays for easy target-selection tasks (Pfefferbaum, Horvath, Roth, and Kopell, 1979; Pfefferbaum *et al.*, 1980; Porjesz and Begleiter, 1981b). This suggests that templates for match/mismatch comparisons are not as readily accessible in chronic alcoholics.
10. Alcoholics manifest the same N1, N2, and P3 ERP characteristics (both amplitude and latency) regardless of task demands and requirements, as follows:
    a. The same low voltage P3 amplitude regardless of task relevance or stimulus unpredictability (Begleiter, Porjesz,

and Tenner, 1980; Begleiter, Porjesz, and Tenner, 1981; Porjesz and Begleiter, 1981a,b; Porjesz, Begleiter, and Garozzo, 1980; Porjesz, Begleiter, and Samuelly, 1980) in alcoholics with and without cortical atrophy (Begleiter, Porjesz, and Tenner, 1980, 1981);

b. the same low amplitude of N2 and P3 regardless of deviance of stimulus from background (Porjesz and Begleiter, 1981a, 1981b);

c. the same delayed N2 latency regardless of ease of discrimination (Porjesz and Begleiter, 1981a, 1981b). These findings suggest that alcoholics have an undifferentiated mode of responding, regardless of task requirements. They appear unable to utilize available information to change their mode of responding.

11. Although some improvement in evoked potential measures has been reported with abstinence from alcohol of 1 month (Salamy *et al.*, 1980) and 4 months (Begleiter and Porjesz, in preparation), EP measures are still aberrant when compared to healthy nonalcoholic volunteers (Begleiter and Porjesz, in preparation; Salamy *et al.*, 1980). It is uncertain at the present time whether these improvements represent subsiding of latent withdrawal concomitants or recovery from brain damage.

CONCLUDING REMARKS

It is apparent from the foregoing review that the brain is a major target site for the actions of alcohol; it is sensitive to acute and chronic alcohol intake (intoxication, neurotoxicity, and tolerance), alcohol removal (withdrawal, physical dependence, hangover), and protracted long-term abstinence (protracted subacute withdrawal, brain damage).

Despite the known susceptibility of the brain to the deleterious effects of alcohol, the etiology of alcohol-related brain damage has not yet been delineated. At present, it is not known whether the brain dysfunction/damage is the direct result of alcohol or acetaldehyde neurotoxicity, indirect effects of alcoholization (e.g., anoxia), concomitants of withdrawal (e.g., stress, ischemia, anoxia), head trauma, or nutritional deficiencies coupled with these alcohol-related factors. There is recent evidence to suggest that alcohol intake in animals results in brain vessel constriction and anoxia (Altura and Altura, 1981). Perhaps only with repeated protracted exposure to alcohol does more permanent brain damage occur. Indeed, it is possible that as Horvath (1975) has

suggested, there is a spectrum of brain damage associated with alcoholism and each of these aforementioned factors may be critical in determining the type of brain damage incurred. Furthermore, recent evidence indicating that sons of alcoholics are at risk for developing alcoholism (Goodwin, 1979), coupled with the evidence that individuals with family histories of alcoholism respond differently to alcohol (Neville *et al.*, 1981), suggest that a genetic and/or constitutional factor may be involved in the development of brain aberrations associated with alcohol abuse. Although the brain deficits observed in chronic alcoholics are presumed to represent years of heavy drinking, it is possible that premorbid brain deficits exist which make these individuals more susceptible to alcohol-related brain damage. This may perhaps explain the puzzling phenomenon that given similar medical and drinking histories, some individuals develop a myriad of severe CNS deficits, while other individuals seem to be resistant to these deleterious effects of alcohol.

As the foregoing review indicates, even among nonalcoholics there is a great deal of interindividual variability in terms of susceptibility to alcohol. Recent evidence from our laboratory suggests that sons of alcoholics (6–14 years of age) display aberrant evoked electrical activity prior to any exposure to alcohol (Begleiter, Porjesz, Bihari, and Kissin, in preparation). Similarly, Neville *et al.* (1981) have recently demonstrated that nonalcoholic adult males with positive family histories of alcohol react quite differently from males without family histories to an acute alcohol challenge in terms of their evoked potentials. Family history may be just one factor influencing the way in which an individual reacts to alcohol, and it remains to be determined to what degree this and perhaps other factors interact to determine an individual's response to alcohol.

Although the etiology of brain damage related to alcoholism remains elusive at present, investigators are focusing on identifying and diagnosing the patterns of brain deficits that accompany alcoholism. This has become possible only in recent years with the advent of computer technology. The development of noninvasive computer techniques permits the identification of structural (CT-Scan) and functional (evoked potential) brain damage in chronic alcoholics. The most recent development of the positive emission tomography (PET) scan technique will perhaps provide additional information about functional brain deficits in alcoholics.

On the basis of these new computerized techniques, it now appears that brain damage due to alcohol abuse is not as localized as had been previously thought. While for many years it had been hypothesized that

the right hemisphere is more damaged by alcohol abuse than the left (Parsons, 1975), it now appears on the basis of CT-Scan techniques that structural brain damage is bilaterally symmetrical (Cala and Mastaglia, 1981). Another surprising result to emerge recently with the use of evoked potential techniques is that alcohol-related brain dysfunction is not limited to cortical areas, as had heretofore been thought. Although neocortical areas indeed appear to be extremely susceptible to alcohol effects, recent evidence also points to areas other than neocortex (e.g., brain stem and hippocampus) as being very sensitive to alcohol. Until recently, it was not possible to make inferences about subcortical brain loci with the use of scalp electrodes. With the advent of new evoked potential techniques (e.g., brainstem potentials), it is now possible to investigate subcortical functioning with a noninvasive scalp electrode. Furthermore, as the origins of the various ERP components recorded at the scalp become elucidated, they suggest the possibility of subcortical sites as the sources of components hitherto believed to originate in neocortical areas. As apparent cortical damage and/or dysfunction has been more readily detected than subcortical damage with available techniques (CT-Scan, neuropsychological tests, EP), researchers have limited their investigations to these more obvious brain sites. However, these may not be the most significant clinically. While various brain loci manifest differential sensitivities to alcohol, (perhaps on the basis of complexity of synaptic connections), it seems that most brain areas that have been investigated in animals are susceptible to alcohol with high enough doses (Walker *et al.*, 1981). In addition, the neurophysiological mechanisms involved in the differential actions of alcohol in the brain are currently being investigated (Siggins and Bloom, 1980) and remain to be elucidated. Further research is necessary to assess the differential sensitivities and mechanisms involved in various brain loci to repeated chronic alcohol exposure in animals in an effort perhaps to elucidate whether there is a progression of brain damage involved in alcoholism. It is still equivocal at present whether in fact there is a continuum of brain deficits in chronic alcoholics (Butters *et al.*, 1977; Glosser *et al.*, 1977; Kapur and Butters, 1977; Ryback, 1971) or whether alcohol-related deficits (Horvath, 1975) are independent phenomena (Tarter, 1975).

While researchers throughout the world testing alcoholics with CT-Scans reveal prevalent cortical atrophy, its clinical relevance remains somewhat questionable as the degree of gross atrophy does not correlate or at best weakly correlates with the degree of intellectual impairment (Earnest *et al.*, 1979; Fox *et al.*, 1979; Ramani *et al.*, 1979). In fact, cortical atrophy has been reported on CT-Scans of such disparate

diseases as schizophrenia (Weinberger *et al.*, 1979), lupus erythematosus (Gonzalez-Scarano *et al.*, 1979), anorexia nervosa (Heinz *et al.*, 1977), and dementia (Huckman *et al.*, 1977). Despite the usefulness of the CT-Scan in pinpointing areas of structural damage, at present this technique does not elucidate underlying pathophysiology; so-called cortical atrophy could represent metabolic and fluid changes known to accompany withdrawal, or specific changes in cell morphology or count.

Unfortunately, the importance of determining which aspects of CNS deficits manifested by chronic alcoholics are due to prolonged withdrawal phenomena and which represent other forms of brain dysfunction distinct from withdrawal symptomatology is often overlooked in the literature. Despite the overwhelming evidence indicating that subacute withdrawal symptomatology persists for long periods of time (Begleiter, DeNoble, and Porjesz, 1980; Begleiter and Porjesz, 1977; Bierley *et al.*, 1980; Chu *et al.*, 1978; Porjesz *et al.*, 1976; Walker and Zornetzer, 1974), investigators continue to examine abstinent alcoholics at various time points after alcohol abuse without taking these factors into account. This issue becomes even more critical when relating to reversibility of brain damage and/or dysfunction following alcohol intake. It is often unclear whether improvement is due to subsiding of concomitants of withdrawal (e.g., edema, fluid metabolism) or recovery from other forms of brain damage, particularly since major changes occur during the first few weeks after withdrawal from alcohol. Some improvement of brain deficits has recently been reported on neuropsychological, electrophysiological, and neuroradiological measures following prolonged abstinence. Despite the partial reversibility of brain aberrations, it is still equivocal whether complete recovery from brain deficits can occur with continued abstinence.

Because alcoholism is a uniquely human condition, the spectrum of physical, psychological, and social problems that interact in the alcoholic is almost impossible to duplicate and investigate in laboratory animals. This makes the investigation of brain damage and dysfunction in alcoholism most difficult. A good deal of clinical and medical data collected about an alcoholic's drinking history depends on his verbal report. However, these data may be unreliable since alcoholics often do not admit the extent of their problem even to themselves. In fact, alcoholics are notorious for providing discrepencies in information within the same questionnaire. Alcoholics reporting longer drinking histories may not in fact be those who actually drink longer. This may perhaps explain why relationships between drinking history variables and measures of brain damage (CT-Scan) or dysfunction (neuropsychological tests, electrophysiological measures) cannot be established.

Although animal data generally report relationships between variables of drinking history (length, amount) and brain observations, results from human alcoholics have been less clear-cut. Perhaps this is because animal experiments are based on homogeneous, genetic pools of animals, where all variables except drinking history are controlled. Animal studies have found that different genetic strains demonstrate differential preference for alcohol intake (Rogers, 1972) and are differentially susceptible to the effects of alcohol. Since alcoholics are not a genetically distinct, homogeneous pool, they may differ in terms of their predisposition for alcoholism. The continued investigation of alcohol-related brain dysfunction is critical if we are to gain a better understanding of the mechanisms and etiology involved in alcoholism. Furthermore, the identification and delineation of the exact nature of clusters of brain deficits in chronic alcoholics, and their possible causes, may perhaps alter the treatment and prognosis of an individual alcoholic.

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