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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Human Evoked Brain Potentials and Alcohol

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IN recent years it has become widely recognized that brain damage and/or dysfunction is prevalent in chronic alcoholics (Begleiter & Platz, 1972; Rankin, 1975). With the advent of the computerized tomography scan (CT scan), the assessment of structural damage in the brains of chronic alcoholics has been greatly facilitated, indicating widened cortical sulci (Ron, 1978; Cala et al., 1978; Cala, 1979; Bergman, 1979; Wilkinson and Carlen, 1980; Begleiter et al., 1980b). However, this technique is presently limited as it permits better visualization of some brain loci, (e.g., cerebral cortex) at the exclusion of others (e.g., brain stem). The relationship between structural damage and level of brain functioning remains tenuous (Ron et al., 1978; Wilkinson and Carlen, 1980; 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; because of the tenuous relationship between brain loci and behavioral functions, it is difficult to infer pathological processes from behavioral deficits. Furthermore, the same behavioral deficits may well reflect the product of different complex neurophysiological processes.

The evoked potential (EP) or event-related potential (ERP) technique offers a unique approach for assessing level of brain functioning as it permits the simultaneous investigation of electrophysiology and cognition. The EP technique consists of recording the electrical response of the brain immediately following each repeated presentation of a brief, sensory stimulus of any modality, and using signal averaging techniques to extract the time-locked evoked activity. The neuroelectric activity that is time-locked to the stimulus is elicited with each stimulus presentation, while the random background "noise" cancels out. This yields a characteristic, highly reproducible waveform, lasting between 250–500 msec. The early components (<100 msec) of the EP reflect stimulus characteristics (e.g., intensity), while the later components are more influenced by psychological factors. ERPs 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 technique is a very sensitive index of the functional integrity of the brain; it differs from the CT scan in that it may reflect subtle changes in brain functioning without accompanying structural changes.

Recording electrical activity from the brain has proven to be the only technique that is differentially sensitive to the various phases of alcohol-related dysfunction, namely: acute and chronic alcoholization, tolerance, withdrawal, and long term brain dysfunction. Therefore, this review will be divided into two major sections, namely: one dealing with acute alcohol effects and the second dealing with chronic alcohol intake. The latter section will be subdivided into two subtopics: (1) short term abstinence (withdrawal) and (2) long term brain damage and possible recovery.

ACUTE ALCOHOLIZATION

The effects of acute doses of alcohol on normal brain functioning have been investigated with the use of evoked potentials in an effort to ascertain some parallel between the effects of acute and chronic alcohol intake on the brain. By examining the differential responsivities of various brain loci to acute doses of alcohol, possible loci of brain dysfunction resulting from chronic alcohol abuse can be identified.

Effect of Acute Alcohol Ingestion on Auditory Brain Stem Potentials

With the advent of the auditory Brain Stem Potential (BSP) technique, subcortical brain

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functioning can be investigated with a noninvasive scalp electrode (Sohmer and Feinmesser, 1967; Jewett, 1970; Jewett and Williston, 1971). These potentials are considered to be "far-field" projections of neuroelectric activity occurring in the auditory pathway (Jewett and Williston, 1971; Plantz et al., 1974), and consist of seven positive peaks. The origins of each of these waves have been delineated from the auditory nerve through the medial geniculate bodies (Jewett, 1970; Lev and Sohmer, 1972; Buchwald and Huang, 1975; Starr and Achor, 1975; Starr and Hamilton, 1976; Stockard and Rossiter, 1977).

Acute administration of alcohol has been found to slow the central conduction times of peaks III, IV, V, and VII in animals (Squires et al., 1978a; Chu et al., 1978) and humans (Squires et al., 1978b). Therefore, these investigators concluded that alcohol affects conduction time in more central structures (beginning at the level of the medulla) but not the auditory end organ.

Effects of Acute Alcohol Ingestion on EPs to Repetitive Stimuli: P1-N1-P2 Components (60–250 msec)

There is a growing literature examining the effects of acute doses of alcohol on human sensory EPs recorded at the scalp, in all sensory modalities. It has been examined using auditory (Gross et al., 1966; McRandle and Goldstein, 1973; Flach et al., 1977; Wolpaw and Perry, 1978; Pfefferbaum et al., 1979b; 1980), somatosensory (Lewis et al., 1970; Salamy, 1973; Salamy and Williams, 1973; Porjesz and Begleiter, 1973), and visual evoked potentials (VEP) (Lewis et al., 1969; 1970; Spilker and Callaway, 1969; Porjesz and Begleiter, 1975; Rhodes et al., 1975; Taghavy et al., 1976; Pfefferbaum et al., 1977).

The major result of these studies is a depression of the late (N1-P2) components, occurring between 100–250 msec (Lewis et al., 1969; Salamy and Williams, 1973; Porjesz and Begleiter, 1975; Rhodes et al., 1975; Taghavy et al., 1976; Pfefferbaum et al., 1977; 1979b). While these later EP components are maximally reduced, earlier components (<100 msec) 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 et al., 1979b). Salamy and co-workers (1973; Salamy and Williams, 1973) concluded that these late component amplitude depressions in average EPs primarily represent decreases in single EP amplitudes, rather than increased latency variability. Furthermore, it has been demonstrated that alcohol produces its maximal amplitude depression over association areas, while primary receiving areas are more resistant to alcohol effects in both somatosensory and visual modalities (Lewis et al., 1970; Salamy and Williams, 1973; Porjesz and Begleiter, 1975; Pfefferbaum et al., 1977; Hyvarinen et al., 1978).

It has been suggested that the differential effect of alcohol on the brain depends on the complexity of synaptic connections (Wallgren and Barry, 1970; Himwich and Callison, 1972; Kalant, 1975); while it is likely that all brain loci are ultimately affected by alcohol, some areas require extremely high doses. There is a growing body of evidence in animals indicating that polysynaptic brain sites such as association cortices and reticular formation are extremely sensitive to alcohol (DiPerri et al., 1968; Nakai et al., 1973; Perrin et al., 1974; Kalant, 1975; Klemm, 1976; Hyvarinen et al., 1978; Begleiter et al., 1980a).

There has been a great deal of interest concerning the differential effects of alcohol on right as opposed to left hemisphere functioning. EPs have been reported to be larger over right than left hemispheres to blank flashes at central locations (Lewis et al., 1970; Rhodes et al., 1975) and at occipital locations (Porjesz and Begleiter, 1975) in healthy volunteers. However, much has been made of small amplitude differences that only occur in some subjects. Differences of this order of magnitude can be due to slight differences in resistance, amplifiers, or electrode placements at homologous sites. In fact, a remarkable degree of interhemispheric symmetry has been reported at identical bilateral electrode placements in very large samples of subjects (Harmony et al., 1973).

Nevertheless, a conclusion shared by studies investigating the acute effects of alcohol on bilateral EPs (Lewis et al., 1970; Porjesz and Begleiter, 1975; Rhodes et al., 1975) is that alcohol reduces hemispheric asymmetry, where present. In our opinion, this is more related to a differential susceptibility of the right hemisphere to the direct depressant effects of alcohol than to any preexisting hemispheric differences. There

is a greater reduction of right hemisphere responses than left following alcohol intake regardless of whether hemispheric asymmetry is apparent or not prior to alcohol ingestion (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. Perhaps this is due to a greater blood flow in the right hemisphere than left (Carmon et al., 1972) (and may be unrelated to cognitive interhemispheric differences) (Dabbs, 1980).

However, these interhemispheric differences in responsiveness to alcohol are rather insignificant when compared to the more marked selective susceptibilities of different brain loci (e.g., central vs. occipital) to alcohol. There is a striking degree of symmetry in the various EP components obtained from homologous scalp locations in terms of the magnitude and time course of depression from alcohol when compared to other scalp regions (Porjesz and Begleiter, 1975). In a study of the time course of alcohol effects over a 2-hr period, Porjesz and Begleiter (1975) found that, while occipital responses recovered after 2 hr, central responses did not.

It is difficult to determine how long after ingestion alcohol has its major effect, as many factors are involved, namely, the dose of alcohol and testing regimens. Low doses of alcohol yielding blood alcohol levels (BALs) of 30–65 mg/100 ml have been found to have little or no significant effect on visual or somatosensory EPs, while high doses yielding BAL's of between 90–110 mg/100 ml greatly depressed amplitudes (Lewis et al., 1969; 1970; Salamy, 1973). Thus, the dose of alcohol administered is directly related to the blood alcohol level and the degree of amplitude depression (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 portion 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, is still unclear at the present time. 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. However, we have observed a great deal of intersubject variability in terms of magnitude and time after alcohol ingestion of peak BAL, as well as magnitude and time of maximum EP depression following a single alcohol dose. These individual differences may in part be accounted for by differences in food ingested prior to testing or constitutional differences. Wagman et al. (1978) have recently reported that BALs vary greatly among chronic alcoholics to the same dose of alcohol. Furthermore, they did not find any EP measures that changed as a function of BAL.

One problem in interpreting data obtained from different laboratories with drug administration is the use of a control group or control condition. Cross-sectional designs where different drugs or placebos are administered to different groups of subjects, while providing valuable information, require the use of inordinately large sample sizes because of the variability of responses to drugs across individuals. The most consistent statistical finding is usually the drug X subject interaction. Some studies use a predrug baseline as a control condition and compare EPs before and after alcohol administration (e.g., McRandle and Goldstein, 1973; Wolpaw and Perry, 1978). Unfortunately, this makes interpretation of results rather difficult as the same late components (N1-P2) that are most sensitive to alcohol are also those that habituate over time. While a predrug baseline is necessary to indicate normal variability within a subject, it is optimal to also use a placebo condition, where the subject acts as his own control in order to determine the specific effects of alcohol.

Effects of Acute Alcohol Ingestion on ERPs in Information-Processing Paradigms: N1 and P3 Components (100–500 msec)

Thus far, we have dealt with studies requiring subjects to passively attend to stimuli while under the influence of alcohol. However, attentional fluctuations cannot be ruled out as interacting with alcohol effects to account for EP amplitude decrements. The same EP component (N1-P2) that is maximally depressed by alcohol varies most with attentional manipulation.

The issue of attentional factors interacting with alcohol effects can be readily investigated with the use of ERP techniques, requiring the subject to be actively engaged in specific tasks during ERP recording. The effects of acute doses of alcohol on ERPs have been recorded during target-selection tasks (Rhodes et al., 1975; Obitz et al., 1977; Kopell et al., 1978; Pfefferbaum et al., 1980; Porjesz and Begleiter, unpublished), requiring the subject to detect a particular rarely occurring target stimulus in a series of frequently occurring nontarget stimuli. ERPs recorded to frequently occurring nontarget stimuli consist of N1-P2 components, but no P3, while 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 employing target-selection paradigms concur that the amplitude of N1 to frequently occurring nontarget stimuli is depressed by alcohol over central areas (Rhodes et al., 1975; Kopell et al., 1978; Pfefferbaum et al., 1980; Porjesz and Begleiter, unpublished), but not occipital areas (Obitz et al., 1977). Marked amplitude reductions have been reported at central leads, regardless of attentional factors (task vs. no task), leading Rhodes et al. (1975) to conclude that, while both attention and alcohol significantly alter ERP amplitude, the effect of attention was of a lesser magnitude than the effect of alcohol on ERP. This is particularly interesting in light of the fact that Obitz et al. (1977) were able to counteract alcohol-slowed reaction times but not ERPs with the introduction of monetary reward. Thus, despite attentional factors, N1 amplitudes are still markedly reduced with alcohol, at least under these experimental conditions. However, a study by Roth et al. (1977) using a memory retrieval paradigm failed to confirm these findings. Roth et al. (1977) conclude that the mobilization of attention may have counteracted alcohol-produced N1 decrements. This difference in results is perhaps due to the difference in task requirements and complexity between target-selection and memory-retrieval paradigms; attention may not be mobilized to the same extent in target-selection designs as in memory-retrieval designs. It is therefore possible that the depressant effects of alcohol can at least be somewhat offset by the complexity of task requirements.

Despite the preponderance of studies examining the effects of alcohol on N1-P2 components, very few studies have attempted to investigate the effects of alcohol on P3. A P3 or P300 component is only elicited under certain specific conditions related to stimulus significance, namely, task relevance, unpredictability, and infrequency (Sutton et al., 1965; 1967; Tueting et al., 1971). Thus, rarely occurring target and nontarget stimuli can elicit P3 components. The characteristics of P3 are unrelated to stimulus parameters, and they can even be elicited without a stimulus (e.g., emitted potentials). In terms of scalp topography, P3 has been found to be maximum over parietal areas (Simson et al., 1976; 1977a; 1977b).

All target-selection paradigms investigating P3 components to rarely occurring nontarget stimuli demonstrate significant P3 amplitude reductions with alcohol (Kopell et al., 1976; Pfefferbaum et al., 1980; Porjesz and Begleiter, unpublished). Of the studies examining P3 characteristics to target stimuli following alcohol ingestion, only Pfefferbaum et al. (1980) do not report P3 amplitude decrements. P3 reductions to target stimuli have been reported to 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). No significant P3 latency shifts have been reported following alcohol ingestion with the exception of Pfefferbaum et al. (1980), who reported small increases of P3 latencies to infrequent target but not nontarget stimuli.

From the foregoing, it can be concluded that the effects of alcohol on normal brain functioning are not as straightforward as was first suspected, but depend on a complex interaction of many factors (dose of alcohol, time of testing, nutritional status, attentional factors). As specific 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. These single dose studies are important in that they provide information about 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.

CHRONIC ALCOHOL ABUSE

The effects of chronic alcohol administration on the EP has been primarily investigated in animals. The animal literature indicates that prolonged alcohol administration produces decrements in EP amplitudes (Bierley et al., 1980) and BSP delays (Chu et al., 1978); these changes are of a lesser magnitude when tolerance develops (Chu et al., 1978). The removal of alcohol creates a rebound hyperexcitability which is characterized by increased EP voltages (Porjesz et al., 1976; Begleiter and Porjesz, 1977; 1979; Hunter and Walker, 1980; Bierley et al., 1980) and extremely shortened BSP latencies (Chu et al., 1978). This central nervous system (CNS) hyperexcitability has been found to persist far beyond clinically overt signs and symptoms of withdrawal (~3 weeks) (Walker & Zornetzer, 1974; Porjesz et al., 1976; Begleiter & Porjesz, 1977; 1979; Chu et al., 1978; Begleiter et al., 1980a; Bierley et al., 1980). The persistence of these electrophysiological changes have been found to be directly related to the length of alcohol exposure (Begleiter & Porjesz, 1977). Abstinent animals that were challenged with a small dose of alcohol 2–5 wk following withdrawal, manifested increased evoked potential amplitudes ((hyperexcitability), while naive control animals exhibited depressed evoked potentials at visual cortex (Porjesz et al., 1976; Begleiter and Porjesz, 1977). It should be noted that evoked potentials of the two groups of animals were identical prior to the challenge dose, indicating that long lasting CNS changes may at times be so subtle that they can only be detected with the use of a challenge dose. As this transient CNS hyperexcitability can mask or interact with other forms of underlying brain dysfunction or damage, it is difficult to separate CNS dysfunctions that are related to withdrawal effects from brain deficits caused by repeated chronic alcohol abuse. In order to examine long term brain damage, it is important to test alcoholics who are abstinent for long periods of time after hyperexcitability has dissipated. As CNS hyperexcitability has been reported to last as long as 3 wk postwithdrawal, this time point will be arbitrarily used to separate what will be considered as "short term" (<3 wk) from "long term" (>3 wk) brain dysfunction for the purpose of this review. Therefore, this section dealing with chronic alcohol abuse will be divided into two separate subsections, namely, those relating to CNS hyperexcitability (<3 wk postwithdrawal) and those relating to long term brain dysfunction or damage and recovery (>3 wk). It should be stressed, however, that this arbitrary time period may not be clinically significant.

Short-Term Abstinence (Withdrawal)

There are very few studies that have examined human alcoholics during acute withdrawal (Begleiter et al., 1974; Wagman et al., 1978), perhaps because of the difficulties involved in testing. In one study in our laboratory (Begleiter et al., 1974) we examined recovery functions of somatosensory evoked potentials during 4 days of intoxication and withdrawal, always recording 10 hr 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. These findings of increased amplitudes of cortical evoked potentials following alcohol withdrawal have been replicated in animals (Porjesz et al., 1976; Begleiter and Porjesz, 1977; Begleiter et al., 1980a; Bierley et al., 1980) and have been confirmed by Coger et al. (1976), Wagman et al. (1978), Lelord et al. (1980), and Porjesz and Begleiter (1979) in alcoholics, following at least 1 wk of abstinence.

Coger et al. (1976) found that alcoholics in "withdrawal" (1 wk after alcohol removal) manifested higher VEP amplitudes (P100-N140) than normal controls. They also found that "stabilized alcoholics" who had been abstinent from alcohol for 3–4 wk exhibited higher VEPs than controls and did not differ from the "withdrawal" group. However, these results were confounded by drug effects, as all alcoholics were on Antabuse (disulfiram) which has recently been reported to increase EP amplitude (Peeke et al., 1979). Nevertheless, it is possible that these increased VEPs resulted from residual withdrawal and, hence, persisting CNS hyperexcitability. Similar findings were also obtained by Wagman et al. (1978), who examined VEPs in detoxified (7–21 days) chronic alcoholics during experimentally controlled alcoholization and withdrawal. They reported increased amplitudes (<130 msec) in alcoholics, 16–17 days following experimentally induced withdrawal, particularly those alcoholics with low slow wave sleep (SWS). However, baseline measures were obtained from 7–21 days after detoxification and were different for the low SWS (mean, 14 days)

and normal SWS groups (mean, 24 days). Lelord et al. (1980) were able to demonstrate that alcoholics abstinent from alcohol for 10 days were more responsive to phantom light than were normal controls. The incidence of emitted potentials was higher in alcoholics than controls. Lelord et al. (1980) concluded that these findings indicate hyperexcitability in the alcoholic sample.

CNS excitability in alcoholics has also been investigated using the augmenter-reducer continuum first studied by Petrie (1967; 1958). Petrie distinguished two types of individuals: augmenters, who tend to amplify stimulation, and reducers, who tend to reduce stimulation. Petrie made the observation that alcoholics tend to be augmenters, and that alcohol ingestion reduces augmentation in augmenters. Buchsbaum (Buchsbaum and Pfefferbaum, 1971) demonstrated that EPs could be used to differentiate between individuals who are augmenters and those who are reducers, with the use of an amplitude-intensity gradient (A-I slope). Augmenters exhibit an increasing VEP amplitude (P100-N140) with increasing stimulus intensity (positive slope), while 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 normal subjects (Spilker and Callaway, 1969; Pfefferbaum et al., 1977; 1979b), by decreasing responses to higher intensities, and also recently with alcoholics (Buchsbaum and Ludwig, 1980). Control subjects (reducers) who were administered alcohol in the same study reacted quite differently, by augmenting their responses. Buchsbaum and Ludwig (1980) conclude that alcoholics perhaps rely on alcohol to inhibit their sensory processes, as their A-I slope most resembled those of sober controls (with reduced sensory stimulation at highest inputs) at the highest dose of alcohol. In fact, alcohol may have a "normalizing" effect on the A-I slope as has been suggested for many other physiological functions (Kissin, 1974), augmenting responses of reducers and reducing responses of augmenters.

The early observations by Petrie that alcoholics tend to be augmenters has been supported by several evoked potential studies (von Knorring, 1976; Coger et al., 1976; Ludwig et al., 1977), particularly those with a family history of affective disorder (Martin et al., 1979). Most of these studies reporting enhanced A-I gradients in abstinent alcoholics test them during the first 2 wk of abstinence when withdrawal symptomatology has not yet subsided. Recently, Buchsbaum and Ludwig (1980) have confirmed the previous findings that alcoholics do not manifest decrements in EP amplitudes to high intensity stimuli. They postulate that this overresponsiveness to high intensities may represent a lack of cortical inhibition in chronic alcoholics. Coger et al. (1976) report that alcoholics in "withdrawal" (1 wk abstinent) exhibited higher right hemispheric A-I gradients than controls and "stabilized" (3–4 wk abstinent) alcoholics. This suggests that, as withdrawal subsides, 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 normal controls. Extrapolating 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 (decreased BSP latencies and increased EP amplitudes and A-I slopes) may last as long as 3 wk postwithdrawal, and possibly longer. The exact time course of subsiding hyperexcitability has not been determined, as the use of medication and length of abstinence are overlooked in many studies. Studies often test patients at widely divergent times (e.g., 13–93 days) after alcohol withdrawal, and then report group data. The phase of recovery from alcohol, and hence the level of CNS reactivity (e.g., hyperexcitability) may be quite different across individuals, making group data relatively meaningless. Testing patients at the same point after alcohol is critical in determining the nature of brain dysfunction, as subsiding CNS hyperexcitability may often camouflage more long lasting forms of brain dysfunction or damage. Even testing patients at the same point after alcohol is not sufficient to ensure that they are in the same phase of recovery from alcohol, as 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. Only longitudinal study can delineate and possibly separate persistent withdrawal deficits from those of underlying long term brain

dysfunction or damage. We are currently undertaking such a project, recording EPs daily in abstinent chronic alcoholics beginning at detoxification.

Long Term Abstinence

Early evoked activity. We have recently recorded auditory BSPs from alcoholics who were abstinent from alcohol for 1 mo (Begleiter et al., 1981). We found that they manifested delays in latencies and central conduction velocities of peaks II–V. These findings are remarkably similar to those found by Squires et al. in animals (1978a) and man (1978b) with acute doses of alcohol. However, the peak delays manifested by their intoxicated human subjects were still within the normal range, while the chronic alcoholics in our investigation (Begleiter et al., 1981) were well beyond the normal range.

This study (Begleiter et al., 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 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.

We are currently investigating whether these BSP aberrations are reversible following 4 mo of abstinence in the same alcoholics. Our preliminary results indicate that following 4 mo of abstinence, despite marked improvements in central conduction times for peaks III–V in the same patients, neural transmission velocities still remain significantly slower than those obtained in normal controls.

We are also presently examining abstinent chronic alcoholics with the use of the visual pattern-reversal EP technique (Begleiter et al., in preparation). This technique is very sensitive to assessing the integrity of the visual system (Halliday et al., 1973a, b; Regan et al., 1976; Halliday, 1978) and can detect very early stages of neurological disorders such as multiple sclerosis, optic neuritis, compression of the optic nerve, etc. (Halliday et al., 1973a, b; 1976; Hennerici et al., 1977). We find that the characteristic positive component, occurring at approximately 100 msec in normal individuals (P100) is abnormally delayed in chronic alcoholics abstinent for 1 mo. Similar findings are currently being obtained by Posthuma (Posthuma, personal communication). Following prolonged abstinence (4 mo), we find that the P100 latency shifts earlier in the same alcoholics, with respect to their previous records at 1 mo; however, this component is still delayed when compared to healthy controls. At present it is premature to equivocally state whether this component ever recovers completely in chronic alcoholics.

Thus, it appears that chronic alcoholics abstinent for long periods of time manifest delayed latencies in electrical activity, suggestive of possible demyelination in both auditory and visual pathways, that may or may not be reversible with prolonged abstinence. The relationship between these measures and drinking histories remains to be determined.

Late evoked activity (ERPs). There is a paucity of studies that have examined the effects of chronic alcohol abuse in long term abstinent (>3 wk) alcoholics. Over the last several years, Beck and his colleagues have recorded VEPs in abstinent chronic alcoholics passively attending to repetitive flashes (Schenkenberg et al., 1972; Cannon, 1974; Beck et al., 1978; Dustman et al., 1979). More recently, investigators have attempted to delineate long term brain dysfunction and possible recovery in abstinent chronic alcoholics using target-selection P3 ERP paradigms, requiring the subject to be actively engaged in a task (Porjesz and Begleiter, 1979; 1980; Begleiter et al., 1980b; Porjesz et al., 1980a; 1980b; Pfefferbaum et al., 1980; Salamy et al., 1980). While all of these studies concur that it is the late components (N1-P2 and P3) that are most aberrant in chronic alcoholics, it should be noted that some differences in results have been reported across different laboratories. The differences in findings across laboratories may perhaps be explained by numerous methodological factors, namely: (1) differences in patient populations tested (e.g., length of abstinence at time of testing, differences in neuropsychological deficits, age, sex, severity of drinking history); and (2) differences in experimental procedures (e.g., passive vs. active paradigms, speed vs. accuracy, task complexity, stimulus modality, ERP electrodes and measurements).

One problem encountered in many of these studies examining alcoholics who are abstinent for long periods is the use of medication, particularly Antabuse (disulfiram). Studies in which Antabuse was administered for long periods of time (Coger et al., 1976; Cannon, 1974; Salamy et al., 1980) do not report late component (N1-P2) amplitude depressions over association cortex. Recently, Peeke et al. (1980) reported increases in ERPs with disulfiram in healthy volunteers. Contamination by drug effects is particularly critical when "recovery" is being examined (e.g., Coger et al., 1976; Salamy et al., 1980), as increased amplitudes at 3–4 wk may be due to the effects of withdrawal, interaction between detoxification and medication, or recovery from brain damage.

For the past several years in our laboratory, we have systematically examined electrophysiological concomitants of information-processing deficits in abstinent chronic alcoholics who are medication-free, with the use of the ERP techniques. In one recent bimodal (visual and auditory) study (Porjesz and Begleiter, 1979), we investigated brain dysfunction by examining the N1 ERP component, a component sensitive to the selection of a relevant or irrelevant channel (in this case stimulus modality). In healthy subjects, the N1 component is enhanced to all stimuli in a relevant channel, and depressed to stimuli in irrelevant channels (Hillyard, 1978). Interspersed among frequently occurring randomized 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 in an otherwise identical stimulus sequence. ERPs were obtained only to the irrelevant frequent single flashes, which were either in the relevant or irrelevant stimulus modality in a given condition; these frequent single flashes elicit N1, but not P3 components, that are differentially enhanced in the relevant channel (stimulus modality).

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 scalp loci. Furthermore, less hemispheric asymmetry (right hemisphere amplitudes larger than left) was evident in the alcoholics than in the controls. These findings with abstinent chronic alcoholics are remarkably similar to the results 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. These ERP results (Porjesz and Begleiter, 1979) obtained while the subject was actively engaged in a task confirm previous findings with repetitive flashes in chronic alcoholics (Schenkenberg et al., 1972; Cannon, 1974).

The advantage of using an information-processing ERP design to assess brain functioning is that it provides additional information comparing responses to identical relevant and irrelevant inputs, not possible with passive EP techniques. Indeed, we found that in contrast to healthy subjects, the amplitude of N1 remained the same in the alcoholics, regardless of whether the stimulus was in the relevant or irrelevant modality. This suggests that chronic alcoholics may be incapable of appropriate "sensory filtering" in that they do not electrophysiologically differentiate 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 visual stimulus-selection ERP paradigm (Porjesz et al., 1980a). 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. In this study, all stimuli were in the relevant channel or modality (and, hence, would be expected to have enhanced N1 components). However, the P3 component would only be obtained to *rarely* occurring stimuli that were either task relevant (target) or irrelevant (novels). Thus, this experimental design tests their ability to probability-match stimuli in terms of their frequency of occurrence. Target and nontarget stimuli were alternated every other block so that ERPs could be compared 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, on the basis of the N1 data, these studies both 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 amplitudes are maximal at scalp (Ritter et al., 1968; Simson et al., 1977a, b). While normal controls manifested differentially enhanced, late P3 components to target stimuli, alcoholics manifested identical low amplitude P3 waves with the same P3 latencies regardless of whether a stimulus was a target or nontarget.

The P300 component of the ERP has been considered to be a manifestation of the orienting response (Ritter et al., 1968; Roth, 1973; Donchin, 1979). Certain nonmodality-specific hippocampal neurons are reported to be involved in the orienting response (Vinogradova, 1970), reacting to significant or novel stimuli and inhibiting responses during habituation to repeated stimuli. Despite its maximal amplitude at the scalp over parietal areas, recent evidence with implanted electrodes in humans suggests that the neural origins of P300 are subcortical (Wood et al., 1979; Halgren et al., 1980) and implicate the amygdala and hippocampus.

Thus, our finding that chronic alcoholics manifest low voltage or even absent P300 components under conditions designed to elicit maximum P3 components may be indicative of hippocampal deficits, although it does not rule out contributions from cortex. The involvement of hippocampus with chronic alcohol intake in the absence of malnutrition has been recently demonstrated in neuropathological (Riley and Walker, 1978; Walker et al., 1980) and electrophysiological (Begleiter et al., 1980a) studies with animals. Long term ethanol consumption has been found to result in the loss of dendritic spines on neurons of mouse (Riley and Walker, 1978) and rat (Walker et al., 1980) hippocampus. In our laboratory, we have demonstrated a susceptibility of evoked potentials recorded from monkey hippocampus to both acute and chronic alcohol intake (Begleiter et al., 1980b).

We have recently become interested in determining the relationship between electrophysiological deficits and structural changes observed in chronic alcoholics (Begleiter et al., 1980b). We selected two groups of alcoholics who had been subjected to CT scans following 1 mo of abstinence: those manifesting a high degree of enlarged cortical sulci (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, and drinking history (duration and amount). ERPs were recorded on the same day as the CT scan and involved the same P3 paradigm previously described (Porjesz et al., 1980a).

We found that both groups of alcoholic patients manifested lower P3 amplitudes to target stimuli than did normal controls, replicating our previous findings with chronic alcoholics not differentiated in terms of CT-scan (Porjesz et al., 1980a). Alcoholics with Pos-CTs had significantly lower (or absent) P3s to target stimuli than did alcoholics with Neg-CTs. In agreement with our previous results (Porjesz et al., 1980a), we found that both groups of alcoholics displayed similar P3 components to all classes of stimuli regardless of task relevance.

These findings suggest that, in man, chronic alcohol abuse not only results in 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 deficits than subcortical aberrations.

We are currently examining the reversibility of ERP and CT-scan deficits in chronic alcoholics abstinent for 4 mo (Begleiter and Porjesz, in preparation). Our preliminary findings indicate some recovery of N1-P2 and P3 amplitudes from their levels at initial testing; however, these voltages are still reduced compared to those obtained from healthy volunteers. Therefore, the potential reversibility of these electrophysiological aberrations remains to be determined.

CONCLUSION

A number of conclusions can be drawn from the foregoing review of the literature dealing with the effects of alcohol on human neurophysiology. One important result to emerge re-

cently is that brain dysfunction resulting from alcohol is not limited to cortical areas, as had heretofore been thought. While cortical areas indeed appear to be extremely susceptible to alcohol effects, recent evidence also points to subcortical sites (e.g., brainstem and hippocampus) as being very sensitive to alcohol. Until recently, it was not possible to make inferences about human subcortical brain loci with the use of scalp electrodes. With the advent of new technology (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 delineated (e.g., P300), they point to possible subcortical sites as the sources of components hitherto believed to originate in cortical areas.

As apparent cortical damage and/or dysfunction can be 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. It now appears that brain damage due to alcohol abuse, while not totally diffuse, is not as highly localized as had been previously thought. While various brain loci manifest differential sensitivities to alcohol (perhaps on the basis of complexity of synaptic connections), it seems that most brain areas which have been investigated in animals are susceptible to alcohol with high enough doses. The differential susceptibilities of various brain loci to repeated chronic alcoholization need further investigation in both animals and man.

The etiology of the development of alcohol-related brain dysfunction or damage is still ambiguous at the present time; whether it is the direct result of alcohol (or acetaldehyde) toxicity, anoxia, ischemia, head trauma, the withdrawal syndrome, or some combination of alcoholism and nutritional deficits still remains to be clarified. It is possible that only with repeated chronic exposures does more permanent brain damage occur.

It is important to determine whether the CNS deficits manifested by chronic alcoholics are due to prolonged withdrawal phenomena or represent brain aberrations separate from withdrawal dysfunctions. Unfortunately, despite the overwhelming evidence indicating that subacute withdrawal persists for long periods of time (Walker and Zornetzer, 1974; Porjesz et al., 1976; Chu et al., 1978; Begleiter and Porjesz, 1977; Begleiter et al., 1980a; Bierley et al., 1980), this issue is mostly ignored in the literature. This question becomes even more critical when relating to possible reversibility of brain damage and/or dysfunction following alcohol intake. It is often unclear whether "reversibility" is due to subsiding of withdrawal or recovery from brain damage, particularly as major improvements in functioning occur during the first few weeks after withdrawal from alcohol; some changes in brain dysfunction have recently been reported in 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. This problem can only be resolved with careful longitudinal study of CNS changes during acute withdrawal and subsequent abstinence, using electrophysiological, neuropsychological, and neuroradiological measures.

At the present time it is not known whether the CNS deficits manifested by chronic alcoholics are a consequence of many years of alcohol abuse or are premorbid to the development of alcoholism, or represent an interaction of the two. Even among alcoholics with similar drinking histories, there are great individual differences in susceptibility to alcohol-related brain deficits. It is possible that some of these CNS deficits may be predisposing factors to alcoholism. In order to resolve this issue, it would be necessary to examine brain dysfunction in subjects at high risk for alcoholism prior to exposure to alcohol. Recent evidence suggests that offspring of alcoholics and hyperactive children have a higher probability of becoming alcoholic than the general population (Goodwin et al., 1973). Prospective studies of these high risk subjects would be critical to determine whether some CNS deficits, in fact, antedate alcohol abuse or are markers to predict potential alcohol abuse.

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