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NEUROPHYSIOLOGICAL FACTORS ASSOCIATED WITH ALCOHOLISM

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INTRODUCTION

Event-related potential (ERP) techniques permit the observation of electrophysiological manifestations of cognitive activity and thereby offer a unique approach for assessing brain function. ERPs are obtained by recording, with noninvasive scalp electrodes, the time-locked brain electrical activity following the delivery of a discrete stimulus to any sensory modality. Signal-averaging techniques permit the extraction of these time-locked neuroelectric signals from the random electroencephalogram (EEG) background "noise," which is canceled out with these procedures. Depending on stimulation properties, experimental paradigms, filter settings, recording sites, feature extraction, and quantitative measurement procedures, these time-locked signals represent overlapping activity emanating from neural generators along the pathways from peripheral end organs to higher cortical integrative centers in the brain. Thus, the functional integrity of many systems in the brain can be assessed.

ERP techniques are also useful in indexing electrophysiological concomitants of complex cognitive tasks (Hillyard et al. 1978; Donchin 1979; Donchin et al. 1978). ERPs consist of characteristic, highly reproducible waveforms. The early components of the waveforms, occurring less than 100 milliseconds after stimulus presentation, reflect stimulus characteristics (e.g., intensity). Because such components are considered to be determined by physical properties of the stimuli, they customarily are referred to as evoked potentials (EPs). In contrast, the later ERP components are influenced more by psychological factors such as the salience of the event.[2]

EPs are extremely sensitive to the various aspects of acute and chronic alcohol administration on the brain, specifically alcoholization, tolerance, withdrawal, and long-term brain effects. Alcoholization is characterized by decreases in EP

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[2]*For a detailed discussion of measurement and application issues of the ERP, the interested reader might consult Begleiter (1979) or Coles et al. (1986).*

amplitudes (Bierley et al. 1980), particularly the negative component (N1) occurring 100 milliseconds after the stimulus (Porjesz and Begleiter 1992), as well as decreases in conduction velocities of both the brain stem auditory evoked response (BAER) (Squires et al. 1978*a*,*b*; Chu et al. 1978) and the positive component occurring at 300 milliseconds (P3) (Schuckit et al. 1988; Porjesz and Begleiter 1992). When tolerance develops, the BAER delays are less pronounced (Squires et al. 1978*a*,*b*; Chu et al. 1978; Zilm et al. 1981), and P3 latency recovers relatively quickly (Schuckit et al. 1988; Porjesz and Begleiter 1992).

Withdrawal is marked by increases in EP voltages and extremely shortened BAER latencies, suggesting underlying central nervous system (CNS) hyperexcitability (Porjesz et al. 1976; Begleiter and Porjesz 1977, 1979; Begleiter et al. 1980*a*; Squires et al. 1978*a*,*b*; Chu et al. 1978; Hunter and Walker 1980; Romani and Cosi 1989; Noldy and Carlen 1990; Neiman et al. 1991). Long-term abstinence following chronic alcohol intake is characterized by depressed EP amplitudes (hyporeactivity) and prolonged BAER latencies and slower conduction velocities (Begleiter et al. 1981; Porjesz and Begleiter 1983, 1985). This chapter provides an overview of the changes associated with alcohol in ERPs and EPs.

SENSORY EVOKED POTENTIALS

BAERs

The BAER provides sensitive measures of subcortical functioning along the auditory pathway with a single noninvasive scalp electrode (Jewett and Williston 1971; Sohmer and Feinmesser 1967). These "far-field" potentials consist of seven time-locked positive peaks. Each peak is presumed to reflect activity at sites along the auditory pathway from the auditory nerve through the brain stem (Buchwald and Huang 1975; Jewett 1970; Lev and Sohmer 1972; Starr and Achor 1975; Starr and Hamilton 1976; Stockard and Rossiter 1977). The latencies of these peaks, as well as their central conduction velocities (time interval between the various sites), are informative in localizing pathology from the eighth nerve to the brain stem. The time interval between peak I and peak V is taken as the measure of brain stem transmission time (Fabiani et al. 1979).

We found that hospitalized alcoholics abstinent for 1 month, without overt signs of neurological damage, manifest delays in latencies and brain stem transmission times of peaks II to V (Begleiter et al. 1981). These results have been replicated in neurologically intact alcoholics (Cassavan et al. 1984), and similar findings have been reported in neurologically impaired alcoholics (Chu and Squires 1980; Chu et al. 1982; Chu and Yang 1987; Haas and Nickel 1981; Nickel and Ludewig 1981; Rosenhamer and Silfverskiold 1980)

The increased transmission time has been postulated to reflect demyelination, a process that has been long suspected in alcoholics (Adams et al. 1959; also see Harper and Kril, chapter 3) and has been observed in rats chronically exposed to alcohol (Moscatelli and Demediuk 1980; also see Lancaster, chapter 19). Although a number of nutritional factors and drink-

ing history are suspected to result in BAER delays, (e.g., years of alcohol abuse, amount consumed per occasion, number and severity of withdrawals), the etiology of abnormal BAERs in alcoholics remains undetermined. There is abundant evidence that nutritional deficits lead to demyelinating diseases such as polyneuropathy (Hillman 1974) and may be necessary for BAER abnormalities (Chu et al. 1978). Overall, these findings indicate that BAER aberrations in alcoholics may be the result of alcohol and/or nutritional factors.

P1

Another useful technique in the early diagnosis of demyelinating disorders in the visual system is the pattern-reversal evoked potential (PREP) technique. This technique consists of the rapid alternation of checkerboard patterns with illuminated and nonilluminated squares. The PREP includes a prominent, positive component around 100 milliseconds (P1) poststimulus change. It is sensitive to changes in the integrity of the visual system (Halliday 1978; Halliday et al. 1973*a,b*; Regan et al. 1976) and is useful as an early diagnostic tool of neurological disorders such as multiple sclerosis, optic neuritis, and compression of the optic nerve (Halliday et al. 1973*a,b*; Hennerici et al. 1977). Abnormal delays in the P1 have been reported in several laboratories in at least 50 percent of alcoholics (Janaky et al. 1980; Porjesz and Begleiter 1983; Posthuma and Visser 1982)

In summary, these early sensory potentials (BAER and P1) are sensitive to alcohol-related aberrations. Delayed latencies in these early potentials are suggestive of possible demyelination of both auditory and visual pathways. For additional information on alcohol-related damage to cerebral white matter, consult Lancaster (chapter 19).

EVENT-RELATED POTENTIALS (ERPS) AND COGNITIVE PROCESSES

ERP techniques have proven useful in indexing electrophysiological concomitants of complex cognitive tasks (Donchin 1979; Donchin et al. 1978; Hillyard et al. 1978). They can be recorded in conjunction with or without overt behavioral responses to both attended and unattended stimuli. In contrast to other imaging techniques, ERPs reflect subtle dynamic millisecond to millisecond transactions that are elicited while the brain is being challenged. Therefore, they are more sensitive to specific brain processes than magnetic resonance imaging (MRI) or computed tomography (CT), both of which typically measure static gross brain damage. ERP abnormalities are often observed in the absence of brain damage as visualized on CT or MRI.

N1 (Nd)

The N1 component is a negative component occurring approximately 100 milliseconds after a stimulus. In healthy individuals, it is larger in response to stimuli in a relevant (or attended) channel and reduced in response to stimuli in an irrelevant channel. The Nd (or negative difference) component is a subtraction between the N1 amplitudes in the waveforms obtained to the attended and unat-

tended channels. Hence, Nd amplitude indexes the selection of a relevant channel and is related to allocation of attentional resources (Hillyard et al. 1973, 1978; Picton and Hillyard 1974).

We examined the ability of abstinent alcoholics to focus on a relevant stimulus modality and inhibit responding to an irrelevant modality by studying the N1 component of the ERP (Porjesz and Begleiter 1979). Alcoholics were presented with sequences of randomized single flashes and single clicks interspersed with rare double flashes and double clicks. For each sequence, they were instructed to count either the double flashes or double clicks, or to ignore all stimuli in otherwise identical stimulus sequences. ERPs were recorded only to the irrelevant single flashes, which were either in the relevant stimulus modality (when double flashes were counted) or irrelevant stimulus modality (when double clicks were counted), depending on the assigned condition. These frequent flashes elicited N1 components that were differentially enhanced in response to stimuli in the relevant channel (stimulus modality). That is, N1 was larger in response to the single flashes if subjects were counting the double flashes as opposed to counting the double clicks.

Using this paradigm, alcoholics demonstrated essentially normal early components (< 100 milliseconds) but significantly reduced late components. As expected, control subjects produced significantly enhanced N1 components in response to stimuli in the relevant as compared to the irrelevant modality. Alcoholics, on the other hand, maintained the same low N1 amplitudes (i.e., showed reduced Nd) regardless of the degree of task relevance. These findings suggest that alcoholics may be incapable of appropriate sensory filtering, being unable to neurophysiologically differentiate between relevant and irrelevant channels. (See Nixon, chapter 10, for further discussion of relevance/irrelevance and efficiency in alcoholics).

Using a similar bimodal experimental paradigm, Patterson et al. (1987) also examined N1 amplitudes to visual and auditory stimuli in abstinent alcoholics. Because these results were modality specific, Patterson et al. attributed the observed pattern to a sensory deficit in alcoholics in the visual but not the auditory modality. The alcoholics in their study also showed less differential enhancement in attended versus unattended visual stimuli than did nonalcoholics. However, this difference failed to achieve statistical significance. This pattern was not observed for auditory stimuli.

In an entirely visual target-selection paradigm involving geometric shapes (see section on P3 for a description), alcoholics were also found to exhibit reduced N1 amplitudes compared to controls (Porjesz et al. 1980). Despite the fact that all the stimuli in this paradigm were in the relevant channel, N1 amplitudes were found to be comparable to voltages expected in an irrelevant modality.

As suggested by the findings of Patterson et al. (1987) discussed earlier, the outcome is quite different in the auditory modality. Similarly, no differences in N1 amplitude between alcoholics and controls were reported by Pfefferbaum et

al. (1991) in both automatic and attended auditory paradigms to the frequent tones or to the rare tones in the attended paradigm. Likewise, Hertz et al. (in press) failed to obtain significant N1 differences in an auditory selective attention task.

Thus, N1 amplitude deficits are apparent in alcoholics only to visual stimuli in visual or bimodal selective attention paradigms. These visual N1 amplitude reductions are obtained in response to both the frequent nontargets and rare targets in the task-relevant channel. These results indicate that alcoholics manifest an impaired ability to selectively attend to a task-relevant sensory channel. These findings suggest that sensory-filtering mechanisms are impaired in alcoholics to visual but not auditory stimuli. Although it appears to be a modality-specific finding, differential task difficulty between auditory and visual selective attention tasks may also contribute to the observed differences.

P3 (P3a, P3b)

Considerable attention has focused on the P3 component of the ERP. The P3 is a prominent positive component occurring between 300 and 500 milliseconds after the stimulus is presented. It is elicited under rather specific conditions related to stimulus significance, namely task relevance (Sutton et al. 1967), unpredictability (Donchin et al. 1978), infrequency (Tueting et al. 1971), and certain motivational factors (Begleiter et al. 1983). P3 characteristics are unrelated to stimulus parameters and can be elicited in the absence of an expected stimulus (emitted potentials) (Klinke et al. 1968).

Two kinds of P3 are often distinguished: P3a and P3b. Most studies address the P3b component, which occurs in response to task-relevant stimuli within the subject's awareness. P3b has a parietal maximum scalp topography (Ritter et al. 1968; Simson et al. 1977*a,b*). In contrast, P3a is obtained in response to rare, deviant, or novel stimuli within a repetitive stimulus train, to which the subject does not attend, and has a more anterior distribution over the scalp. The most standard paradigm used to elicit a P3 is the "oddball" or target-selection paradigm. In this paradigm, subjects are asked to attend to rare target stimuli (press a button or count) while ignoring the other stimuli. ERPs in response to frequently occurring (nontarget) stimuli elicit N1 components but no P3s. Rarely occurring stimuli (targets) elicit both N1s and P3s.

In an early study mentioned previously (Porjesz et al. 1980), we studied the P3 component in abstinent alcoholics with a visual paradigm involving geometric shapes. Rare and frequent geometric shapes (e.g., triangle, square) and rare novel irregular shapes were interspersed in a random sequence. Subjects were instructed to press a button in response to the occurrence of the rare geometric shape only. Target and nontarget stimuli were alternated in blocks enabling the recording of ERPs in response to the same shape (e.g., triangle) when it was both a target and nontarget.

Using this task, alcoholics exhibited reduced or absent P3 components in response to the target stimuli without

latency delays. This finding was most pronounced over the parietal areas where the P3b is maximal (Ritter et al. 1968; Simson et al. 1977*a*,*b*). As one might expect, controls manifested differentially enhanced late P3 components in response to target stimuli. However, alcoholics produced identical low amplitude P3 waves with the same P3 latencies, regardless of whether the stimulus was a target or nontarget. Thus, the major ERP aberration shown by alcoholics was the lack of differentiation between their responses to relevant and irrelevant inputs, and the low voltages of their event-related activity. The finding of reduced P3 amplitudes in alcoholics in visual oddball paradigms has been replicated in several laboratories (Emmerson et al. 1987; Patterson et al. 1987; Pfefferbaum et al. 1991; Porjesz et al. 1987*a*). This pattern suggests underlying brain dysfunction that impairs sensory-filtering and probability-matching processes.

However, to clarify the role that difficulty of discrimination might play in determining the amplitude of P3, another visual oddball task was used (Porjesz et al. 1987*a*). P3 components were obtained in response to two targets: an easily discriminated target line stimulus that was 90 degrees from the vertical nontarget and a target that was difficult to discriminate, being only 3 degrees from the nontarget. Consistent with previous work, alcoholics produced significantly decreased P3 amplitudes. This diminished amplitude was more apparent for the easy (90-degree) target than the difficult (3-degree) target, with controls manifesting extremely large voltages in response to the easy targets. Furthermore, the amplitude difference between the easy and difficult targets was significant for controls but not for alcoholics.

Among controls, enhanced P3 in response to the easy target would be predicted based on a number of studies demonstrating that the more deviant a rare stimulus is from the background (i.e., 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 a P3 amplitude difference between the easy and difficult targets in the alcoholic group reflects an uncertainty of the correctness of their response.

Using a visual oddball task, Emmerson et al. (1987) found that only the amplitude of the N2-P3 peak-to-peak measure differentiated alcoholics from nonalcoholics. However, in order to control for a number of subject variables, they examined only alcoholics who were younger than 40 and who had been abstinent at least 1 month. Other researchers have also reported decreased P3 amplitudes without latency delays (Patterson et al. 1987; Pfefferbaum et al. 1991).

In addition to standard oddball paradigms, other visual P3 tasks also elicit diminished P3 amplitudes in alcoholics. Using a visual paradigm requiring subjects to respond on some trials (Go), but not on others (No-Go), Pfefferbaum et al. (1987) obtained lower P3 amplitudes in alcoholics under the Go but not under the No-Go conditions. In addition, the scalp distribution of P3 was more similar

across electrodes for alcoholics, compared to the controls in the Go but not in the No-Go condition.

In a visual P3 paradigm involving incentive factors, Porjesz et al. (1987*b*) reported lower P3 amplitudes to equiprobable high-incentive stimuli in alcoholics when compared to controls. No differences in latency were observed. Latency corrected average procedures indicated these results were not due to latency jitter in the average but rather were due to lower single trial voltages. This result was recently replicated by Pfefferbaum et al. (1991) in both visual and auditory oddball paradigms.

The relation between visual P3 amplitude (in the geometric shape paradigm described above) and structural brain damage as assessed by CT scans was investigated by Begleiter et al. (1980*b*). Two groups of alcoholics were studied: those who exhibited severely widened cortical sulci (Pos-CT) and those who did not manifest such widening (Neg-CT). The two groups did not differ in terms of age, education, and duration or amount of alcohol consumed. Alcoholics in the Pos-CT group showed significantly lower P3 amplitudes to target stimuli than did Neg-CT subjects. Both groups displayed significantly smaller P3 amplitudes to targets than did control subjects. Neocortical shrinkage alone cannot explain the results of diminished P3 amplitudes in alcoholics because both Pos-CT and Neg-CT alcoholics manifested these electrophysiological deficits.

Evidence from intracranial recordings in humans implicates both the medial temporal lobe (Halgren et al. 1980; McCarthy 1985; Smith et al. 1986; Stapleton 1985; Wood et al. 1980, 1984) and source(s) within the frontal lobe (McCarthy 1985) as contributing to P3 generation. These findings coupled with the rather small effect of unilateral temporal lobectomy on scalp P3 during auditory discrimination tasks (Stapleton 1985; Wood et al. 1984) suggest that multiple brain sites may be involved. Given the data suggesting frontal lobe involvement in alcohol-related cognitive deficits, it may be that the reduced P3 amplitudes in alcoholics reflect frontal lobe damage (also see Oscar-Berman and Hutner, chapter 6).

The P3 results from auditory paradigms are not as consistent as those from visual paradigms. In an early auditory oddball study in which speed of response was stressed, Pfefferbaum et al. (1979) reported no difference in P3 amplitudes between an older sample of alcoholics and healthy controls. However, alcoholics did exhibit delayed P3 latencies. In contrast, Patterson et al. (1987) found decreased auditory and visual P3 amplitudes to target stimuli in the absence of latency delays in a bimodal study. In a subsequent study (Parsons et al. 1990), this team failed to replicate the finding with female alcoholics.

In a more recent study, Pfefferbaum et al. (1991) reported that P3 amplitudes to attended target stimuli were significantly different between alcoholics and controls. This difference was found in both visual and auditory oddball paradigms. Consistent with the study by Porjesz et al. (1987*b*), single-trial latency adjustment

procedures indicated that these amplitude differences were due primarily to signal size differences between the two groups rather than greater single-trial latency variability. Single-trial analysis of P3 amplitude indicated that the reductions in amplitude were due to smaller voltages on individual trials, not the number of P3s in the average. Furthermore, standard deviations of single-trial P3 amplitude indicated no significant differences between groups for either the auditory or visual paradigm. P3 latencies were delayed in alcoholics only to attended auditory targets. There were no P3 delays to attended visual targets or unattended rare auditory stimuli.

The study by Pfefferbaum et al. (1991) clarifies earlier differences in the literature regarding whether alcoholics manifest P3 latency delays in oddball tasks. Latency delays were reported in an auditory oddball paradigm (Pfefferbaum et al. 1979) but not in a visual paradigm (Pfefferbaum et al. 1987; Porjesz et al. 1980). Similarly, Pfefferbaum et al. (1991) reported response time (RT) delays in alcoholics to auditory but not visual attended targets. Finally, Porjesz et al. (1987*a*) found P3 latency delays in alcoholics in an easy, but not a difficult, discrimination task.

Perhaps, rather than being modality specific, P3 latency delays in alcoholics are sensitive to the difficulty of discrimination between targets and nontargets. Auditory oddball tasks are generally easier than visual tasks. In the Porjesz et al. (1987*a*) study, controls demonstrated significantly earlier P3 latencies to easy discriminations as compared to difficult ones. However, alcoholics did not manifest differences in P3 latency contingent on discrimination difficulty. In alcoholics, the P3 latency delays in response to the easy targets were prolonged, comparable to latencies found with a difficult discrimination task. These results suggest that alcoholics found both tasks difficult and adopted an undifferentiated mode of responding regardless of task requirements.

Considering this literature, the most consistent electrophysiological measure that differentiates alcoholics from controls is their decreased P3 amplitude to targets for visual tasks (particularly at the parietal-midline electrode). Although these findings have also been observed in the auditory modality, they are not robust. It should be noted that evidence indicates that the visual and auditory P3s are generated at different brain loci. Furthermore, many different kinds of P3 are elicited under various experimental conditions with different brain generators (Ruchkin et al. 1990). The P3 components discussed thus far are obtained to attended stimuli of significance (i.e., to which the subject must make a response, P3b). However, a small number of studies have examined automatic processes and the more frontal P3 component associated with such processes, the P3a.

In an inattentive auditory oddball paradigm, Pfefferbaum et al. (1991) found that although P3a amplitudes in response to rare unattended stimuli were smaller in alcoholics than in controls, this result did not reach significance. However, this study used a somewhat small sample size

(23 alcoholics and 21 controls). Perhaps with a larger sample, the difference would have attained statistical significance.

Using an almost identical automatic auditory oddball paradigm in our laboratory, Realmuto et al. (in press) found that alcoholics exhibited significantly lower P3 amplitudes than did controls to rare unattended tones. In this study, 63 male alcoholics were compared to 27 controls. In addition to differences in sample size, another possible difference between the two studies is that our laboratory used tones of two different frequencies, whereas Pfefferbaum et al. (1991) used a white tone burst as the rare stimulus. Therefore, the two studies may have differed in terms of stimulus deviance of the rare stimulus relative to the background stimuli.

Both studies agree that there are no significant differences in midline topography (i.e., distribution across frontal, central or parietal midline sites) between the two groups in terms of the P3a amplitude to unattended rare stimuli. Furthermore, although Pfefferbaum's results were not significant, the direction of the difference was consistent with the findings of Realmuto et al. (in press).

Using a selective attention auditory task, Hertz et al. (in press) also found significantly lower P3 amplitudes for both attended and unattended rare tones in alcoholic subjects compared to controls. P3 latencies were delayed in response to rare nontarget but not to rare target auditory stimuli.

Thus, these studies suggest that automatic match/mismatch processes as well as control processes are impaired in alcoholics, although automatic processes may not be as significantly compromised. Alcoholics apparently are less able to distinguish deviant stimuli from repetitive background stimuli. It is possible that either the template for comparison is not formed or retained, or that the match/mismatch processes themselves are impaired in alcoholics.

N2 (MMN)

Another component of the ERP that has been examined in alcoholics is the N2 component. N2 is a negative component that occurs approximately 200 milliseconds after the stimulus is presented. The N2 component of the ERP is modality specific, with a maximum amplitude over occipito-parietal scalp regions for the visual modality, and over central areas for the auditory modality. The latency of N2 is assumed to be an early index of stimulus evaluation time (Renault and Lesevre 1979): the easier a discrimination, the earlier the latency of the N2 (Gaillard and Lawson 1980; Ritter et al. 1979; Towey et al. 1980). The latency of N2 is superior to RT as an index of stimulus evaluation time because it is not confounded by the motor response. RT, on the other hand, is a complex measure of speed of information processing, contingent on the end product of stimulus evaluation, response selection and organization, and the motor response. Although reports in the literature suggest delayed RTs in alcoholics (Bertera and Parsons 1973; Talland 1963; Vivian et al. 1973), RT studies alone cannot ascertain which aspect(s) of this complex process are slowed in alcoholics.

To examine speed of stimulus evaluation in alcoholics, we designed a visual-spatial ERP RT paradigm in which the relation between difficulty of discrimination, N2 latency, P3 characteristics, and RT could be examined. The task, described previously under the section on P3, consisted of frequently occurring vertical lines (nontargets) and two kinds of rare targets, an easy-to-discriminate target and a difficult target (Porjesz et al. 1987*a*). Subjects were required to press a button to all nonvertical stimuli.

As expected, controls exhibited delayed N2 latencies to difficult discriminations. In contrast, N2 latency did not reflect discrimination difficulty in alcoholics. Alcoholics produced similar N2 latencies regardless of discrimination difficulty. Moreover, the N2 latency occurred significantly later in the alcoholics than in the controls for both the easy and difficult discriminations. These data suggest that alcoholics found both discriminations difficult and required more time for stimulus evaluation. Interestingly, the latency difference between groups was more apparent for the easy discrimination than for the difficult discrimination. These results imply that alcoholics need disproportionately more time to make an easy discrimination than to make a difficult discrimination when compared to controls.

Consistent with previous work (Naatanen et al. 1980), the amplitude of the N2 was related to degree of stimulus deviance for controls, being larger for easy as compared to difficult discriminations. However, for alcoholics, the N2 amplitude was unaffected by discrimination difficulty.

There were no significant differences in RT between the groups although alcoholics did tend to have shorter RTs. Alcoholics also produced more errors, both in terms of false alarms and misses. However, the group differences on these measures also failed to achieve significance. This response pattern suggests an emphasis on speed as opposed to accuracy (Kutas et al. 1977) and implies that alcoholics adopted a different response strategy than controls. These data also suggest a lack of inhibition in alcoholics as reflected by their apparent inability to withhold responding until the certainty of accuracy or correctness has been established.

Using an auditory oddball paradigm in which subjects attend to one set of stimuli (e.g., tones in one ear) but not another (e.g., tones in the other ear), Realmuto et al. (in press) found that controls exhibited larger N2 amplitudes in response to the rare relevant stimuli than did alcoholics at frontal and central midline sites, but not at the parietal midline site. It is noteworthy that, in these auditory paradigms, an N2 component is also obtained in reponse to unattended rare stimuli; Naatanen et al. (1980) named this negativity to unattended deviant stimuli the mismatch negativity (MMN). Realmuto et al. (in press) found that MMN amplitude was significantly reduced in alcoholics. These investigators also found a delayed latency for alcoholics that approached significance when age was parceled out (MMN latency was found to be directly related to age).

Latency delays of the N2 component have been reported in alcoholics compared to controls in a visual oddball paradigm in which only young alcoholics (<40 years of age) were accepted for study (Emmerson et al. 1987). Hertz et al. (in press), using an auditory paradigm requiring subjects to attend to a rare tone in one ear, also found that the latency of N2 was prolonged in alcoholics. In this latter study, N2 delays were obtained for both attended targets and rare nontargets.

In general, alcoholics manifest prolonged N2 latencies. Assuming that N2 latency indexes discrimination difficulty, these prolongations in N2 suggest that alcoholics have more difficulty with stimulus evaluation than controls. Thus, on the basis of both the N2 and P3 ERP component characteristics, alcoholics seem to have less efficient match/mismatch processes than controls and, hence, more difficulty evaluating the potential significance of a stimulus.

N400

Another late ERP component that has received attention is the N400 component. The N400 is a late negative component with a maximum at centro-parietal scalp, occurring approximately 400 to 600 milliseconds after incongruous semantic stimuli. Moreover, the N400 varies with semantic incongruity, phonological priming or matching, and the extent of search in memory (for review, see Kutas and Van Petten 1988).

In our laboratory, we recently completed a study examining the N400 component in alcoholics (Porjesz and Begleiter in preparation *a*). The paradigm consisted of a lexical decision task requiring subjects to indicate as rapidly as possible whether a letter string was or was not a word. Words preceded by semantically related words were more quickly recognized than were those preceded by unrelated words or nonwords. This semantic priming effect suggests that the semantic features of each word remain activated on subsequent trials, thereby reducing the threshold of hypothetical word recognition for words sharing some semantic features. The primed words used in this paradigm were simple antonyms (e.g., hot-cold).

In this semantic processing paradigm, the N400 component is elicited to the unprimed but not the primed words in normal subjects. Our results indicate that alcoholics respond to primed words in a fashion similar to unprimed words; that is, they exhibit N400s to primed as well as unprimed words. This impaired priming mechanism suggests possible semantic memory deficits in alcoholics. This study is the first to demonstrate semantic memory deficits in alcoholics using electrophysiological measures.

Memory Potentials

In order to examine mnemonic processes that are not semantically mediated, we used a modified delayed matching-to-sample task using stimuli that were difficult to name (Begleiter et al. in press). Pairs of visual line stimuli (S1 and S2) that were either simple (consisting of a few line elements) or complex (consisting of a greater number of elements) were

randomly presented. On half of the trials, the test stimuli (S2) were identical to S1; on the remainder, S2 was distinctly different from S1. After each presentation of S2, the subject indicated whether S2 matched S1 (choice RT). Accuracy and speed were equally emphasized. This paradigm elicits a waveform with a relatively negative peak around 170 milliseconds followed by a relatively positive peak around 240 milliseconds. These peaks are maximal over right temporal areas and are termed visual memory potentials (VMP).

Begleiter et al. (submitted) found that in both alcoholic and control subjects, RTs were significantly shorter for matching versus nonmatching stimuli for both the simple and complex stimuli. RTs were shorter for simple as opposed to complex stimuli. The results were similar for alcoholics and controls. However, alcoholics produced longer RTs than did controls in all conditions. As one might expect, based on the RTs, the latency of VMP was earlier for controls than for alcoholics. Matching stimuli were processed more quickly than nonmatching stimuli as evidenced by significantly earlier VMPs for matching stimuli.

VMPs yielded higher voltages to the nonmatching S2 compared to the matching S2 in controls. However, alcoholics did not manifest any difference on these measures between matches and nonmatches. This finding suggests that alcoholics could not differentiate stimuli previously seen from novel stimuli.

These data implicate deficits in the processes underlying matching-to-sample tasks in alcoholic subjects. Alcoholics' responses to nonmatching stimuli were aberrant in both their lower voltage and their lack of differentiation from identity (matching) responses.

Overview of ERPs

In summary, the results from studies examining the N2, P3, N400, and memory potential (VMP) components of the ERP indicate that match/mismatch processes are impaired in alcoholics. P3 studies indicate that alcoholics are not only deficient in their response to task-relevant target stimuli (P3b) but also to task-irrelevant rare stimuli (P3a). Thus, P3 deficits may be attributable to malfunctioning of more rudimentary match/mismatch processes, in which the template is either lost or absent. Coupled with those results indicating delays in N2 latency, these studies indicate that alcoholics have difficulty with stimulus evaluation. Specifically, it appears that match/mismatch processes are less efficient in alcoholics, are less well localized, and require more time to occur.

In addition to the implications of the P3 paradigms, potential memory dysfunction in alcoholics is also suggested by the results from semantic priming and matching-to-sample paradigms. Alcoholics respond to primed words in a similar fashion as to unprimed words (N400). Similarly, they do not electrophysiologically discriminate between matching and nonmatching visual stimuli (VMP).

Thus, the memory dysfunction suggested by these studies appears based on deficits in rudimentary match/mismatch processes, regardless of type of stimuli or the automaticity of the task. The deficit is

most apparent under mismatch conditions, wherein controls exhibit large differential responses. However, it should be noted that additional research designed to specifically address the relation of these electrophysiological findings to direct tests of memory function is still needed and is ongoing in our laboratory.

RECOVERY OF EVOKED BRAIN POTENTIAL DEFICITS WITH ABSTINENCE

The EP is extremely sensitive not only to alcohol administration but also to subsequent withdrawal and long-term abstinence. Because of this sensitivity, it is difficult to determine whether brain dysfunction shown by alcoholics is the direct result of their time in recovery. Earlier EP studies investigating recovery in alcoholics considered the first 3 or 4 weeks after detoxification and often overlooked the effects of medication administered during treatment (e.g., Coger et al. 1976; Salamy and Faillace 1980). In these studies, disulfiram and/or chlordiazepoxide, both of which affect EP voltages, were administered to recovering alcoholics. Increased EP amplitudes have been reported in volunteers who were experimentally administered disulfiram (Peeke et al. 1979). Therefore, it is difficult to ascertain in these early studies whether the changes in amplitude reported were due to the effects of subsiding withdrawal, medication, an interaction between detoxification and medication, or recovery from brain damage. Furthermore, the study by Coger et al. (1976) used a cross-sectional design in which different groups of alcoholics were tested at two time points.

Recent studies of auditory EPs indicated that withdrawal was marked by increased N1-P2 peak-to-peak components, particularly in seizure-prone alcoholics (Neiman et al. 1991; Noldy and Carlen 1990). Similarly, Romani and Cosi (1989) reported larger N1-P2 peak-to-peak components as well as shorter P3 latencies in an auditory oddball paradigm during alcohol withdrawal.

In order to examine whether EP aberrations observed in alcoholics would improve with prolonged abstinence, we examined abstinent alcoholics who were part of a long-term inpatient rehabilitation program (Porjesz and Begleiter 1985). Only alcoholics who were not administered medication were studied at two time points following withdrawal: at 3 to 4 weeks after withdrawal and at 4 months after withdrawal. BAERs and auditory and visual P3s were recorded on both occasions. At the initial testing, we found that BAERs and conduction velocities were delayed. However, following 4 months of abstinence, alcoholics showed improved BAER morphology, shortened latencies, and improved conduction times.

The relative importance of abstinence from alcohol and of nutritional factors in recovery remains undetermined. For example, throughout the long-term treatment in our rehabilitation program, patients received extensive vitamin therapy and most likely improved their nutritional status.

Also, the role of withdrawal cannot be overlooked. CNS hyperexcitability may be

followed by a period of subacute hypoexcitability. This hypoexcitability may be manifested as a prolongation of brain stem latencies caused by aberrant fluidizing effects on the membranes that may result in edema. It has been reported that edema resulting from osmotic stress can lead to demyelination (Feigen and Budzilovich 1978, 1980; Kleinschmidt-Demasters and Norenberg 1981; Lewis 1976; Yates 1976; also see Harper and Kril, chapter 3; Lancaster, chapter 19).

We could examine reversibility only in alcoholics who completed the 4-month treatment program. Importantly, these individuals were those less impaired at initial assessment. Therefore, we cannot conclude that recovery occurs in all alcoholics regardless of degree of initial impairment. It remains to be determined whether recovery occurs as a function of degree of initial impairment, whether greater impairment requires longer recovery time, or whether there is an asymptotic level of reversibility, regardless of recovery time and initial impairment.

Despite the improvement in the BAER with prolonged abstinence, neither ERP morphology nor P3 amplitude improved following 4 months of abstinence in these same alcoholics. The waveforms and decreased P3 voltages to both auditory and visual stimuli were strikingly similar at initial test and retest. There was also no improvement in the differential enhancement of P3 amplitudes on the basis of task relevance to target stimuli. These results suggest that low P3 voltages may not be reversible or may recover more slowly.

Evidence from our laboratory indicates that alcoholics manifest low voltage P3 amplitudes even following extremely prolonged sobriety (Porjesz and Begleiter 1985). We examined recovering alcoholics with 3 to 10 years of sobriety and found that they still exhibited low voltage P3 components, although BAERs were normal. Thus, it appears that some electrophysiological aberrations improve with sobriety, whereas other anomalies do not. As will be discussed in following sections, one likely hypothesis is that abnormalities which fail to improve with sobriety may precede the development of alcoholism and may actually serve as biological markers for or predisposing factors to alcoholism.

FAMILY HISTORY OF ALCOHOLISM AND ERPS

Brain abnormalities observed in alcoholics are generally assumed to be due to the toxic effects of alcohol on the brain, nutritional deficits, or an interaction of alcohol and nutritional-related factors. However, as will be shown in this section, recent evidence suggests that some of these aberrations may antecede the development of alcoholism and may even be related to a genetic predisposition to alcoholism.

Alcoholics

A great deal of interest has been directed to examining the meaning of the diminished P3 voltages observed in alcoholics. Because the P3 component does not appear to recover with prolonged abstinence (see previous section) and its characteristics appear to be genetically determined (Polich and Burns 1987), the

role of chronic alcohol abuse on P3 characteristics has come into question.

Recently, there have been some investigations of the role of family history in determining the amplitude of the P3 component in alcoholics. In our laboratory, we have repeatedly observed that alcoholics manifest significantly lower visual P3 amplitudes than controls. However, the majority of alcoholics in our studies have a positive family history for alcoholism. Therefore, clarifying the relative importance of alcohol versus family history can be difficult. For example, in a recent study we found, as expected, reduced P3 amplitudes in alcoholics (Porjesz et al. 1987*a*). When the alcoholic sample was divided into family history positive (FHP) and family history negative (FHN) subgroups, FHP groups tended to exhibit lower visual P3 amplitudes. However, this difference approached but did not achieve significance (Henry et al. in preparation). In order to be considered FHP in this study, it was only necessary to have an alcoholic father. It is likely that the small sample sizes and having only one alcoholic relative contributed to the nonsignificant results.

Patterson et al. (1987) reported significantly smaller auditory and visual P3 amplitudes in alcoholic males compared to controls. In addition, they found that FHP alcoholics manifested the lowest P3 amplitudes. P3 differences between FHP and FHN alcoholics were significant in the visual modality but only approached significance in the auditory modality. Patterson et al. (1987) attribute their findings to family history. However, they did not eliminate the possible contributions of lifetime drinking history or pattern of alcohol consumption in accounting for P3 amplitude decrements.

Recent evidence from a PATH analysis performed by Pfefferbaum and colleagues (1991) indicates that family history of alcoholism rather than lifetime consumption determines whether alcoholics manifest low P3 amplitudes. They found that FHP male alcoholics had reduced P3 amplitudes for both visual and auditory oddball paradigms compared to FHN alcoholics. P3 amplitude to attended targets was significantly correlated with the number of first-degree relatives with drinking problems for both the auditory and visual RT paradigms. This decreased amplitude was found to be independent of lifetime alcohol consumption in FHP alcoholics.

Thus, there is substantial evidence that reduced P3 amplitudes observed in alcoholics are a function more of family history than chronic alcohol ingestion per se. Perhaps, earlier differences between laboratories regarding P3 findings are, in part, due to differences in the compositions of the alcoholic samples (i.e., the number of FHP versus FHN subjects).

However, it should be noted that all of these studies were conducted using alcoholic subjects. This design makes it difficult to separate the consequences of years of chronic alcohol abuse from other factors. Therefore, a more direct approach to investigating this issue looks at FHP individuals who have not abused alcohol.

Offspring of Alcoholics

Evidence from population genetics studies indicates that sons of alcoholic fathers are

four times more likely to develop alcoholism than are sons of nonalcoholic fathers (Goodwin 1979; Goodwin and Guze 1974). This heightened probability exists even when they are separated from their biological parents soon after birth (Cloninger et al. 1981). Studies of male adoptees in Scandinavia indicate that the biological rather than the adoptive parent is predictive of later drinking problems (Bohman 1978; Cadoret and Gath 1978; Cadoret et al. 1980; Goodwin et al. 1973; Goodwin and Guze 1974). Furthermore, the concordance rate for alcohol abuse between identical twins is almost double the rate for fraternal twins (Kaij 1960), and patterns of alcohol consumption are highly concordant among identical twins (Partanen et al. 1966; Jonsson and Nilsson 1968; Loehlin 1972). Thus, these data, covering several decades of research, suggest that genetic factors predispose sons of alcoholic fathers to alcoholism.

There is a good deal of evidence indicating that characteristics of both the EEG and ERP are also genetically determined. For example, the production of fast EEG activity is genetically transmitted (Vogel 1970; Young et al. 1972; Propping 1977). In various studies, Vogel reported on the hereditary nature of several variants (monomorphic alpha, low voltage EEG, EEG with alpha and beta diffusely mixed, EEG with fronto-precentral beta) (Vogel 1970; Vogel et al. 1986). Vogel maintains that the low voltage and regular alpha EEG are inherited via an autosomal dominant mode, whereas the poor alpha or diffuse beta variants are under polygenic control (Vogel 1970).

In addition to EEG patterns being genetically determined, there is also evidence that ERPs are under genetic control. Monozygotic twins manifest ERP waveforms that are as concordant with each other as EPs obtained from the same individual tested twice (Dustman and Beck 1965; Surwillo 1980). EPs recorded to flashes of different intensities have also been reported to be under genetic control (Buchsbaum and Pfefferbaum 1971). Furthermore, the P3 component of the ERP is more similar in identical twins than in unrelated controls (Polich and Burns 1987).

Given the genetic control of brain electrophysiology, the apparent genetic influence on the development of alcoholism, and the data suggesting alcohol-related abnormalities in brain electrophysiology, it is likely that a genetic predisposition to alcoholism is manifested in brain function. Thus, the study of the offspring of alcoholics, referred to as high-risk (HR) individuals, constitutes an important area of research. HR studies are important because they may provide information regarding preexisting abnormalities in brain electrophysiology that may indicate an increased susceptibility to alcoholism and/or the negative consequences of alcohol on brain function (i.e., alcohol-induced brain damage).

For over a decade, we have been studying ERPs in HR subjects. In our first study, the HR group consisted of 7- to 13-year-old alcohol-naive sons of alcoholic fathers (Begleiter et al. 1984). Their fathers had been diagnosed as alcoholic (DSM-III criteria) and had received prior

treatment for alcoholism. Boys whose mothers either ingested alcohol during pregnancy or who drank excessively after birth were excluded. The low-risk (LR) group was comprised of healthy normal boys matched with the HR group on age and socioeconomic status. LR subjects were included only if they had no first- or second-degree relatives with a history of alcoholism or other psychiatric disorder. Only boys with neither medical problems nor exposure to alcohol or other substances of abuse were included.

A complex visual head-orientation paradigm was used to elicit the P3 component. The target stimulus was a rarely occurring aerial view of the head with the nose and either the right or left ear present, rotated in one of two possible positions (up or down). These targets were interspersed randomly among nontargets (ovals). Subjects were required to press one of two switches to the targets, indicating whether the right or left ear was presented, as quickly and accurately as possible. In the "easy" condition, the head was facing forward (nose up on the screen) and the left or right ear appeared on the same side as the appropriate button. In the "difficult" condition, the head was facing back (nose down on screen) and the left or right ear appeared on the side opposite the corresponding button. P3 amplitudes were significantly smaller in the HR compared to the LR group in response to all target stimuli. This group difference was most obvious at the parietal electrode (where P3 is maximum) for the difficult condition. Principal component analyses with varimax rotation (PCAV) performed on the data indicated that only the factor representing the P3 component was significantly different between the HR and LR groups.

Begleiter et al. (1987*b*) studied another group of sons of alcoholics to determine whether the reduced P3 amplitudes observed in HR subjects were modality or task specific. A modified auditory oddball task was used requiring subjects to press a button in response to rarely occurring tones presented at a random rate; accuracy was stressed over speed. Twenty-three matched pairs of FHP and FHN males between the ages of 7 and 16 were studied. They were carefully interviewed to ascertain that they had no prior exposure to alcohol or illicit drugs. The fathers of the HR boys met criteria for "male-limited," Type 2 alcoholism (Cloninger 1987). Specifically, the fathers indicated early onset of alcoholism and a high rate of recidivism (often accompanied by petty criminality), and required extensive treatment. Additionally, the HR boys came from families with high densities of alcoholism. Extending previous work with visual stimuli, FHP boys exhibited reduced auditory P3 amplitudes. Thus, reduced P3 amplitudes in HR subjects do not appear to be task or modality specific and appear to be present under speed and accuracy conditions.

Another laboratory (Whipple et al. 1988, 1991) used a continuous performance test (CPT) to examine ERPs in prepubescent HR boys. In the first study, they used a visual paradigm consisting of a complex series of visual stimuli that changed along three dimensions–shape,

color, and number. The subject silently counted each time a stimulus identically matched the one preceding it on all three dimensions. In agreement with both Begleiter et al. (1984) and O'Connor et al. (1986, 1987), Whipple et al. (1988) reported a reduction in the amplitude of the late positive complex, including the P3 component. Later studies in the same laboratory have replicated these findings (Noble 1990; Whipple et al. 1991).

We have recently replicated our original findings in an older sample (18 to 23 years of age) of HR male subjects (Porjesz and Begleiter 1990). The sample consisted of 25 male offspring of carefully diagnosed male alcoholics and was selected from high-density alcoholic families (mean number of alcoholic family members = 4). Furthermore, individuals whose mothers abused alcohol before, during, or after pregnancy were excluded. Controls were matched to the sons of male alcoholics on the basis of age, education, and socioeconomic status. Controls were selected from families with no history of alcohol abuse or alcoholism in either first- or second-degree relatives. FHP and FHN subjects were carefully matched on drinking history, including duration and quantity–frequency information.

In this study, we used the previously described visual-spatial paradigm involving easy and difficult line discriminations (see section on P3 in alcoholics for description). The results indicated that P3 amplitude was significantly lower in HR subjects compared to controls. This pattern replicates our previous findings (Begleiter et al. 1984, 1987*b*) with an older sample of HR subjects and also replicates the work of O'Connor et al. (1986, 1987) and Whipple et al. (1988, 1991). The largest differences in P3 amplitude between the groups occurred in response to the easy target, to which the LR groups produced extremely large P3s. These results parallel those obtained in alcoholics using the same paradigm (Porjesz et al. 1987*a*). This P3 amplitude difference between groups was most apparent at Pz and Cz electrodes.

Most recently, using another auditory target selection task, we observed that adolescent HR males manifest lower amplitude P3s than LR males (Porjesz and Begleiter in preparation *a*). In this paradigm, rare or frequent tones were randomly presented rather quickly (600 to 800 milliseconds) to either the right or left ear. The rare tones to a specific ear were designated as targets, and the subject pressed a button in response to these as quickly as possible. The same rare tones to the other ear were ignored.

In the absence of other differences between groups (N1 amplitude), HR males showed lower amplitude P3 components to both the rare attended (P3b) and unattended (P3a) tones. These findings indicate that HR subjects did not make probability matches as well as LR subjects. In an inattention auditory oddball paradigm, P3a amplitude was also reduced in HR adolescent males. In this experimental design, subjects read a book during the binaural presentation of rare and frequent tones.

In summary, this literature indicates that P3 is reduced in HR males in response to both attended and unattended

stimuli, and in response to both easy and difficult discriminations in both visual and auditory modalities. Despite the general consensus that P3 amplitudes are lower in HR males, some studies such as those conducted by Polich and Bloom (1987, 1988) and Baribeau et al. (1987) have failed to replicate these findings.

Baribeau et al. (1987) examined HR and LR subjects who were further subdivided according to amount of alcohol consumed (heavy versus light drinkers). They used an auditory selective attention paradigm in which rare (500 Hz) and frequent (600 Hz) tones were randomly presented to either the right or left ear at a random rate (630 to 880 milliseconds). Subjects were instructed to count the signals in one ear and ignore those in the other ear.

HR subjects in this study did not exhibit reduced P3 amplitudes. However, the light drinkers in the HR group manifested smaller (though not significantly smaller) P3s in the inattention condition. These results suggest that when attention is mobilized, P3 deficits are not apparent in the attended channel. Perhaps the reduction of P3 amplitude in the unattended channel would reach significance with a larger number of subjects. As mentioned previously, we have found reduced P3 amplitudes in response to rare tones in the unattended channel in HR subjects with a paradigm similar to this one.

In this same study (Baribeau et al. 1987), HR subjects exhibited significantly larger N1 components than did LR subjects in the attention condition. This finding may indicate that the HR subjects in their study paid more attention to the stimuli than did the LR subjects, perhaps because the tone discrimination was perceived as being more difficult to the HR subjects.

It is important to note that the subject sample in this study represents an older group of HR individuals. There is a rather large age range (19 to 35) with mean ages of 27 (HR-heavy drinking), 22 (HR-light drinking), 24 (LR-heavy drinking), and 25 (LR-light drinking). These HR subjects may have passed the age of risk, rendering the sample unrepresentative of groups at high risk for alcoholism. This observation may be particularly applicable because those who already manifested alcoholic problems were excluded. If by this age they have not developed alcohol-related problems or become alcoholic, the likelihood is that they will not. Thus, this group may represent a skewed sample of HR subjects, perhaps endowed with protective mechanisms. Certainly, their larger N1 component suggests they are atypical.

Related to the issue of possible protective mechanisms, it is interesting that Hill et al. (1988) reported increased cognitive efficiency in nonaffected siblings of alcoholics. They observed shorter P3 latencies in these nonaffected siblings and suggested this finding reflected some protection against the development of alcoholism in so-called HR subjects.

A number of studies using college students with positive family histories of alcoholism have been conducted by Neville and colleagues (Elmasian et al. 1982; Neville and Schmidt 1985; Schmidt and Neville 1985) and Polich and colleagues (Polich and Bloom 1986, 1987,

1988; Polich et al. 1988; Schuckit et al. 1988) at the University of California at San Diego. These studies have produced interesting yet conflicting results.

Following the administration of either alcohol or a placebo, differences in P3 characteristics have been found between HR and LR subjects. Elmasian et al. (1982) studied the P3 component of the ERP in HR and LR male college students (ages 20 to 25) under placebo and low and high doses of alcohol. After alcohol or placebo administration, they reported significant P3 amplitude decreases in the HR compared to the LR subjects. Elmasian et al. (1982) explained their results in terms of differential expectancies for alcohol characterized by different brain events. The investigators also suggested that the results may be due to higher than normal alcohol intake in the mothers of the HR subjects. Unfortunately, different sets of subjects were used for each dose, and there were only five pairs of subjects per group. Therefore, accurate interpretation is difficult. Interestingly, the placebo effect was not replicated in later work in this same laboratory (Polich and Bloom 1988).

In a another study from the same laboratory (Neville and Schmidt 1985), the late positive component (LPC) of the ERP in HR individuals was investigated without the ingestion of any liquid. In this study, mothers of all subjects were interviewed with respect to their alcohol and drug use, and the experimental design eliminated expectancy effects. Group differences in the LPC were still obtained.

In another study, Schmidt and Neville (1985) investigated ERPs in HR males while they were engaged in a visual language task. They found that the N430 component (the component related to semantic processing; see section on N400) was significantly smaller in the HR men than in LR men. Moreover, in the HR group the latency of N430 was directly related to the amount of alcohol consumed per occasion. These fascinating results imply that neuronal function associated with language processes are affected by family history, and that there is an interaction between family history, alcohol consumed, and N430. We are currently examining HR subjects with a semantic priming paradigm.

Polich and Bloom (1987, 1988) and Schuckit et al. (1988) did not find P3 amplitude differences between groups of FHP and FHN male college students. Using an auditory oddball paradigm, Schuckit et al. (1988) did not find any ERP differences between FHP and FHN prior to ethanol ingestion or following a placebo dose. Following a high dose of ethanol (1.1 mL/kg), P3 latency delays returned to baseline measures more rapidly in FHP men. This finding suggests that some electrophysiological differences between FHP and FHN individuals are apparent only in response to ethanol challenges. These differences in response to ethanol challenge may represent an innate tolerance in the FHP subjects.

An inverse correlation between the amount of alcohol consumed (drinks per sitting) and the amplitude of P3 was found by Polich and Bloom (1987) without the administration of alcohol. However, this relation was apparent only

for a difficult auditory intensity discrimination task in FHP subjects. Although there was a trend in this direction for FHN subjects, it was not significant. The authors concluded that FHP subjects are more sensitive to the effects of alcohol than FHN subjects. When a similar intensity discrimination study was performed in the visual modality, no correlation between P3 characteristics and amount of alcohol typically consumed was found (Polich et al. 1988). However, in a later study designed to replicate Elmasian et al. (1982), Polich and Bloom (1988) not only failed to replicate the placebo effect, but reported a correlation between P3 latency and amount of alcohol consumed for both FHP and FHN subjects.

The relation between P3 characteristics and drinking history is as yet an unresolved issue in other laboratories as well. O'Connor et al. (1986) reported no relation between any P3 characteristic and drinking history. However, Steinhauer et al. (1987) did obtain a correlation between P3 latency and drinking history.

One possible explanation for the lack of significant results from the San Diego groups involves the mode of assessment of alcoholism in the fathers and the clinical assessment of their families in general. A questionnaire is completed by the son about his father's and first- and second-degree relatives' alcohol and psychiatric history. To be scored as FHP, only one positive symptom regarding the father's alcoholism is required. Thus, it is possible that in a large percentage of subjects, the offspring are not offspring of alcoholics but rather of heavy or moderate drinkers. This classification procedure weakens the possibility of obtaining ERP differences between FHP and FHN groups. Therefore, it is conceivable that there is more agreement in the literature dealing with subjects at risk for alcoholism than had been heretofore suspected.

Although it has been hypothesized that discrepancies in results between laboratories may be due to task difficulty, recent evidence fails to support this contention. O'Connor et al. (1987), using two tasks at different levels of task difficulty, obtained identical results with both paradigms. Begleiter and his colleagues replicated their finding of a lower P3 amplitude in HR subjects without ingestion of alcohol in four different paradigms thus far. Those used are a complex visual response-compatibility/incompatibility design (Begleiter et al. 1984), an auditory modified oddball paradigm (Begleiter et al. 1987*b*), a visual discrimination paradigm (Porjesz and Begleiter 1990), and an auditory Hillyard paradigm (Porjesz and Begleiter in preparation *b*). It is important to note, however, that task difficulty is not necessarily a continuum along which P3 results can be explained. Some aspects of task difficulty alter P3 characteristics, whereas others do not. For example, difficulty of stimulus discrimination alters P3 characteristics, but response selection does not.

We have recently investigated the effects of alcohol on visual ERPs in HR and LR subjects (Porjesz and Begleiter 1992). Twenty-four pairs of male HR and LR subjects between the ages of 19 and 24 received either a placebo or one of two

alcohol doses (0.5 mL/kg or 0.8 mL/kg). The visual ERP paradigm involving easy and difficult line discriminations described earlier was used. ERPs and measures of levels of intoxication were obtained prealcohol and at 20, 60, 90, and 130 minutes following alcohol ingestion. Blood alcohol levels (BALs) were monitored at 10-minute intervals throughout the session. No significant differences were obtained between groups in terms of BALs or intoxication ratings.

As reported previously, the P3 amplitude was reduced in HR subjects relative to LR subjects to all target stimuli, but particularly to the easy target, prior to alcohol consumption. Alcohol ingestion did not affect the difference in amplitude between groups. Although there was a tendency for alcohol to depress the amplitude of P3 in both groups, this depression did not achieve statistical significance.

However, during the ascending phase of the BAL, the HR group showed a larger percent decrement in P3 amplitude than the LR group to both target stimuli. This pattern may indicate greater sensitization in the HR group on the ascending phase of the BAL (Newlin and Thomson 1990). Similarly, we found more of an increase in slow alpha activity on the ascending limb, indicating sensitization, in HR subjects following an alcohol challenge (Cohen et al. in press).

No significant difference in the latency of P3 occurred between groups prior to alcohol ingestion. The latency of P3 occurred significantly later in response to the difficult compared to the easy discrimination target in both groups. The high dose of alcohol increased the latency of P3 to the difficult target in both groups at all but occipital electrodes. This effect was maximal between 60 and 90 minutes postalcohol, that is, at peak and early descending BALs. Although the HR and LR groups did not differ in terms of initial alcohol-induced P3 latency delays, the HR group appeared to recover more quickly to prealcohol ranges. This finding replicates the work of Schuckit et al. (1988) who reported that FHP males recover more quickly from alcohol-induced P3 latency delays.

The N1 amplitude was significantly decreased by alcohol ingestion beginning at 20 minutes, particularly for the nontarget stimuli at occipital electrodes. This result was more pronounced for the LR than the HR group. Although the N1 to nontargets remained depressed in the LR group throughout the test, it recovered by 90 minutes in the HR group. These results suggest that the HR subjects exhibited an innate tolerance to alcohol, as compared to the LR group. Under alcohol conditions, the N1 amplitude was only partially reduced in response to the easy target and did not decrease in response to the difficult target.

These results support the finding by Roth et al. (1977) that attentional factors can counteract the alcohol-related decreases in N1, and the findings by Campbell and Lowick (1987) that the largest alcohol effects were obtained when attention was least mobilized (nontarget conditions).

The differential effect of alcohol on N1 is an important difference between HR and LR groups and parallels the behav-

ioral results reported by Schuckit et al. (1988). These results suggest that HR subjects exhibit more acute tolerance than LR subjects. Whereas there was a tendency for HR subjects to drink more frequently than the LR subjects and to consume more alcohol per sitting, neither of these differences reached statistical significance. However, we cannot conclude whether this N1 effect is due to innate or acquired tolerance.

This literature indicates that ERPs provide sensitive indices of state and trait variables involved in alcoholic consumption and that specific components of the ERP are differentially sensitive to various aspects of alcohol-related effects. Additional research must be conducted to determine whether subjects with low P3 amplitude before alcohol ingestion also manifest less N1 response to alcohol, and whether these individuals are in fact at higher risk for alcoholism.

Thus, an important question concerns the identification of which differences in electrophysiological function antecede alcoholism and which differences are consequences of years of heavy alcohol consumption. To address this question, we have investigated in nonalcoholic sons of alcoholics many different EP characteristics that are aberrant in chronic alcoholics. In one study discussed earlier regarding P3 changes (Begleiter et al. 1987*a*), we also assessed BAERs in LR and HR subjects. In contrast to the P3 findings, we did not observe any significant differences in BAER measures between LR and HR subjects. Thus, BAER abnormalities observed in alcoholics appear to be consequences of chronic abuse, whereas the P3 amplitude differences appear to be independent of alcohol consumption and may represent trait differences. This finding is underscored by the recovery of the BAER but not the P3 with prolonged abstinence. We are currently examining in HR subjects other ERP components that are aberrant in alcoholics (e.g., MMN, P3a, N400, and VMP).

As noted earlier, the lack of consensus of results among laboratories may at least in part be attributed to differences in subject populations. The only definition of risk for alcoholism that these studies share is that at least the father must have been "alcoholic." Therefore, the density of alcoholism within the family fluctuates across studies. If only the individual's father and no other first- or second-degree relatives are alcoholic, this may not increase the genetic risk for alcoholism but may indicate a phenocopy or sporadic case. Furthermore, the clinical criteria for diagnosis of alcoholism in the father and the manner in which his alcoholism is assessed contribute to differences in the samples studied. Some studies require only one symptom of alcoholism in the father to qualify for inclusion into the FHP group. Therefore, the HR groups in some studies may include offspring of nonalcoholic but heavy or problem drinkers. As previously mentioned, this broad criterion weakens the loading of familial alcoholism and makes it less likely that significant differences between groups will be obtained.

Problems such as comorbidity for other psychiatric problems are also treated

differently in various studies and may contribute to the disparate results. Individuals manifesting comorbid psychiatric diagnoses (e.g., antisocial personality or affective disorder) may be excluded from some studies yet be included in others.

Because alcoholism is a heterogeneous disease, HR groups in different studies may be composed of varying numbers of offspring of different "types" of alcoholism (e.g., Type 1, Type 2). This mixing of types may complicate outcomes because various types of prealcoholic offspring may manifest different electrophysiological patterns before and/or after alcohol administration.

Often, the HR subjects examined are beyond the age of risk, or the stringent screening criteria rule out potential prealcoholics. This selection procedure results in so-called "high risk" subjects who may actually be at low risk for developing alcoholism.

Selection criteria as applied to control subjects must also be carefully examined when comparing the results of these studies. Finally, subject variables such as age, education, and socioeconomic status may influence outcome in both HR and control samples and must be examined to eliminate possible confounds.

Obviously, subject selection remains a major problem in HR research. Ideally, the HR sample consists of young children without prior exposure to alcohol who are offspring of alcoholic fathers from families in which alcoholism is prevalent; these alcoholic fathers should be diagnosed directly.

SUMMARY AND CONCLUSIONS

Electrophysiological research using a variety of paradigms has revealed that a number of ERP components (i.e., N1, P3, N2, MMN, N400, and VMP) are aberrant in alcoholics under certain conditions. Each of these ERP components is sensitive to different aspects of information processing. However, when reviewed as a whole, the literature suggests that alcoholics do not electrophysiologically differentiate between relevant and irrelevant, target and nontarget, easy and difficult, primed and unprimed, familiar and unfamiliar, or even same and different stimuli. Indeed, they maintain the same ERP characteristics (both amplitude and latency) regardless of stimulus or task requirements.

Unfortunately, the neural origins of most ERP components are not known. Therefore, it is difficult to identify which brain areas of alcoholics are most compromised using this technique. Increasing evidence indicates that multiple brain areas contribute to scalp-recorded ERPs. Given the neuropsychological data suggesting involvement of the frontal lobes, it is tempting to speculate that the common component of these ERPs originates in frontal areas. Indeed, as reviewed there is evidence implicating frontal contributions to P3. Additionally, the MMN is thought to have contributions from frontal areas. Furthermore, despite its origins in inferior temporal regions, recent work from our laboratory indicates frontal contributions to the P240 component. Certainly from a theoretical and rational level, the match-mismatch processes themselves (e.g., the ability to differentiate relevant

from irrelevant) appear to be a frontal function.

Future work must continue the focus of separating those brain aberrations that antecede alcohol abuse from those reflecting years of heavy drinking. The delineation of specific neurophysiological deficits in abstinent alcoholics and children at risk for alcoholism may be of fundamental importance in the identification of possible genetic marker(s) for differential responsiveness to alcohol and/or the development of alcoholism per se.

However, to accomplish these goals, long-term longitudinal studies are needed to assess HR individuals as they pass through the age of risk. At present, there is no compelling evidence that subjects showing reduced P3 amplitude are, in fact, destined to become alcoholics. Longitudinal family studies are underway and, hopefully, these studies will elucidate the link between electrophysiological aberrations and the development of alcoholism. Finally, although it is increasingly obvious that genes are an important component in the development of certain types of alcoholism, the role of environment and its interaction with genes cannot be overemphasized. Comprehensive studies must address all of these factors if we are to more completely understand the etiology of and consequences of alcohol abuse.

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