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Effects of Alcohol on Electrophysiological Activity of the Brain

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Event-related potential (ERP) techniques offer a unique approach to assessing brain function as they permit the simultaneous observation of electrophysiology and cognition. ERPs are obtained by recording with noninvasive scalp electrodes brain electrical activity after the delivery of a discrete stimulus to any sensory modality. Signal-averaging techniques permit the extraction of these time-locked neuroelectric signals (event-related potentials) from the random background "noise" (EEG). Depending on stimulation properties, experimental paradigms, filter settings, recording sites, feature extraction, and quantitative measurement procedures, these 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 with this sophisticated, noninvasive neurophysiological technique that has exquisitely sensitive temporal resolution.

In addition to being sensitive to sensory aspects of information processing, ERP techniques have proven to be very useful in indexing electrophysiological concomitants of complex cognitive tasks (Donchin 1979; Donchin et al., 1978; Hillyard et al., 1978). ERPs consist of characteristic, highly reproducible waveforms lasting between 250 to 500 msec. The early components (occurring before 100 msec) that reflect stimulus characteristics (e.g., intensity) are referred to as the evoked potential (EP), whereas the later components that are more influenced by psychological factors are called the ERP.

Evoked Brain Potentials and Alcoholism

EPs are extremely sensitive to the various aspects of acute and chronic alcohol administration on the brain, specifically alcohol ingestion, tolerance, withdrawal,

and long-term brain effects. In general, alcohol ingestion is characterized by major decreases in EP amplitudes (Bierley et al., 1980), particularly the N1 component (Porjesz and Begleiter, 1992), as well as by prolongations in conduction velocities of both the brainstem auditory evoked potential (BAER); (Chu et al., 1978; Squires et al. 1978a,b) and the P3 component (Porjesz and Begleiter, 1992; Schuckit et al., 1988). When tolerance develops, these BAER delays are less pronounced (Chu et al., 1978; Squires et al. 1978a,b; Zilm et al., 1981) and P3 latency recovers more quickly (Porjesz and Begleiter, 1992; Schuckit et al., 1988). Withdrawal is marked by increases in EP voltages, as well as extremely shortened BAER latencies, suggesting underlying CNS hyperexcitability (Begleiter and Porjesz, 1977, 1979; Begleiter et al., 1980a; Chu et al., 1978; Hunter and Walker, 1980; Neiman et al., 1991; Noldy and Carlen, 1990; Porjesz et al., 1976; Romani and Cosi, 1989; Squires et al., 1978a,b). Long-term abstinence after chronic alcohol intake is characterized by depressed EP amplitudes (hyporeactivity), prolonged BAER latencies, and slower conduction velocities (Begleiter et al., 1981; Porjesz and Begleiter, 1983, 1985).

Sensory Evoked Potentials

Brainstem Auditory Evoked Responses (BAERs). The BAER provides sensitive measures of subcortical functioning along the auditory pathway with a single noninvasive scalp electrode (Jewett, 1970; Jewett and Williston, 1971; Sohmer and Feinmesser, 1967). These far-field potentials consist of seven time-locked positive peaks, each presumed to reflect activity at sites along the auditory pathway from the auditory nerve through the brainstem (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 accurate in localizing pathology from the eighth nerve to the brainstem. The time interval between peak I and peak V is taken as the measure of brainstem transmission time (Fabiani et al., 1979).

In our laboratory we have found that hospitalized alcoholics, abstinent for 1 month without overt signs of neurological damage, manifest delays in latencies and brainstem transmission times of peaks II to V (Begleiter et al., 1981). These results have been replicated in neurologically intact alcoholics (Cadaveira et al., 1991; Cassvan et al., 1984; Diaz et al., 1990), and similar findings have been reported in neurologically impaired alcoholics (Chu and Squires 1980; Chu and Yang, 1987; Chu et al., 1982; Haas and Nickel, 1981; Nickel and Ludewig, 1981; Rosenhamer and Silfverskiold, 1980).

The increase in neural transmission time has been postulated to reflect the process of demyelination, which has long been suspected in alcoholics (Adams et al., 1959) and has been observed in rats chronically exposed to alcohol (Moscatelli and Demediuk, 1980). Although both drinking history (years of alcohol abuse,

amount consumed per occasion, and the number and severity of withdrawals) and nutritional factors are suspected to result in BAER delays, the etiology of abnormal BAERs in alcoholics remains to be determined. There is abundant evidence that nutritional deficits lead to demyelinating diseases, such as polyneuropathy (Hillman, 1974). Animal data suggest that factors other than chronic alcohol exposure are necessary to produce BAER abnormalities (Chu et al., 1978), as chronic alcohol ingestion in the absence of nutritional deficits in laboratory animals was not sufficient to cause BAER delays after withdrawal. Taken together, these findings suggest that BAER aberrations in alcoholics may be the result of alcohol and/or nutritional factors.

P1 (P100). Another promising EP technique in the early diagnosis of demyelinating disorders in the visual system is the pattern reversal or pattern evoked potential (PEP) technique. In this technique checkerboard patterns are alternated rapidly such that illuminated and nonilluminated squares alternate with successive presentations. This technique is sensitive in assessing the integrity of the visual system (Halliday, 1978; Halliday et al., 1973a,b; Regan et al., 1976) and is useful as an early diagnostic tool of such neurological disorder as multiple sclerosis, optic neuritis, and compression of the optic nerve (Halliday et al., 1973a, b; Hennerici et al., 1977). This technique elicits a positive component around 100 msec (P100 or P1) poststimulus change. Abnormal delays in the occurrence of the P100 have been reported in several laboratories in at least 50% of alcoholics. (Janaky et al., 1980; Porjesz and Begleiter 1983; Posthuma and Visser, 1982).

On the basis of these early sensory EPs, it seems that chronic alcoholics manifest delayed latencies in early evoked potentials suggestive of possible demyelination in both auditory and visual pathways.

Event-Related Potentials (ERPs) and Cognitive Processes

ERP techniques have proven to be very 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 behavior or, even when no behavioral response is required, to both attended and unattended stimuli. Thus, the ERPs provide sensitive indices of the functional integrity of various systems in the brain. In contrast to other imaging techniques, ERPs reflect subtle dynamic millisecond-to-millisecond transactions that are elicited while the brain is being challenged and hence are very sensitive to specific brain processes. (The EEG reflects ongoing electrical activity, whereas MRI and CT scans indicate static gross brain damage.) ERP abnormalities are often observed in the absence of brain damage as visualized on CT scan or MRI.

ERP techniques require the subject to be engaged in a task, usually an information-processing activity. Depending on the exact paradigm, these tasks elicit specific ERP components with known characteristics and topographies across the scalp. These components can be manipulated predictably in healthy individuals

(in terms of their amplitudes and latencies), and a substantial literature documenting each component has evolved (Donchin et al., 1978; Hillyard et al. 1978).

N1 (Nd). The N1 component occurs approximately 100 milliseconds after a stimulus; it is larger in response to stimuli in a relevant (or attended) channel (e.g., stimulus modality) and is reduced to stimuli in an irrelevant channel in healthy individuals. The Nd (or negative difference) component is sensitive to the difference in N1 amplitude between an attended and unattended channel. Hence, Nd amplitude indexes the selection of a relevant or irrelevant channel and is related to the allocation of attentional resources (Hillyard et al., 1973, 1978; Picton and Hillyard, 1974).

We were interested in examining the ability of abstinent alcoholics to focus on a relevant stimulus modality and to 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 (when double flashes were counted) or irrelevant (when double clicks were counted) stimulus modality for a given condition. These frequent flashes elicited N1 components that were differentially enhanced to stimuli in the relevant channel (stimulus modality).

Alcoholics manifested significantly reduced late (>100 msec) but not early components with this paradigm. These results are similar to findings in healthy individuals after the ingestion of a single dose of alcohol (Lewis et al., 1969; Porjesz and Begleiter, 1975; Rhodes et al., 1975), suggesting that the neurophysiological brain dysfunction observed in abstinent alcoholics may resemble brain functioning in healthy individuals under the influence of alcohol. As expected, control subjects manifested significantly enhanced N1 components to stimuli in the relevant as compared to the irrelevant modality. Alcoholics, on the other hand, maintained the same low amplitudes of N1, regardless of the degree of task relevance. Furthermore, the differential voltage to attended compared to unattended channels (Nd) may be more revealing about the nature of brain function than the absolute voltages to either the relevant or irrelevant stimuli. Therefore, these findings suggest that alcoholics may be incapable of appropriate "sensory filtering," as they do not differentiate neurophysiologically between relevant and irrelevant channels.

Using a very similar bimodal experimental paradigm, Patterson et al. (1987) replicated our findings of diminished N1 amplitudes to visual but not auditory stimuli in abstinent alcoholics. As these results were modality specific, Patterson and co-workers attribute these findings to a sensory deficit in alcoholics in the visual but not auditory modality. Although the alcoholics in this study showed less differential enhancement in attended versus unattended visual stimuli than did nonalcoholics, this finding approached but did not reach statistical significance.

In a purely visual target-selection paradigm involving geometric shapes in our laboratory (see the section on P3 in alcoholics 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.

The findings are quite different in the auditory modality, as suggested by the findings of Patterson et al. (1987). 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. Similar findings were obtained in our laboratory by Hertz et al. (in press) in an auditory selective attention task, where the subject had to attend to one ear and ignore stimuli in the other.

Taken together, it seems that N1 amplitude deficits are only apparent in alcoholics to visual stimuli in visual or bimodal selective attention paradigms. These visual N1 amplitude reductions are obtained 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 as evidenced by a lack of enhancement of the N1 amplitude by the Nd component. These findings suggest that sensory-filtering mechanisms are impaired in alcoholics to visual but not auditory stimuli. Although it seems to be a modality-specific finding, this impairment could be the result of differential task difficulty between auditory and visual selective-attention tasks.

P3 (P3a, P3b). A great deal of attention has focused on the P3 component of the ERP, a prominent positive component occurring between 300 to 500 milliseconds after the stimulus. It can only be 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), as well as motivational factors (Begleiter et al., 1983). P3 characteristics are unrelated to stimulus parameters, and they can even be elicited in the absence of an expected stimulus (emitted potentials) (Klinke et al., 1968).

Two kinds of P3 have been identified: P3a and P3b. Most studies in the literature deal with the P3b component, which occurs to task-relevant stimuli within the subject's awareness. P3b has a parietal maximum scalp topography (Ritter et al., 1968; Simson et al., 1977a,b). In contrast, P3a is obtained to rare, deviant, or novel stimuli within a repetitive stimulus train to which the subject does not attend; it has a more anterior distribution over the scalp. The most standard paradigm used to elicit a P3 is the so-called oddball or target-selection paradigm, in which the subject is asked to attend to rare target stimuli (press a button or count) and to ignore the other stimulli. ERPs to frequently occurring nontarget stimuli elicit N1 components, but no P3s, whereas rare target stimuli elicit both N1s and P3s.

Several years ago, we studied the P3 component in abstinent alcoholics with a visual paradigm involving geometric shapes. Common geometric shapes (e.g.,

triangle, square) and rare, novel, irregular shapes were interspersed in a random sequence, and the subject was instructed to press a button on the occurence of the rare geometric shape only. Target and nontarget stimuli were alternated in blocks, enabling the recording of ERPs to the same shape (e.g., triangle) both when it was a target and when it was the nontarget.

Using this visual target-selection paradigm we found that alcoholics manifested reduced or absent P3 components to the target stimuli without latency delays. This finding was most pronounced over parietal areas where the P3b is maximal (Ritter et al., 1968; Simson et al., 1977a,b). Furthermore, although controls manifested differentially enhanced late P3 components to target stimuli, alcoholics manifested identical low amplitude P3 waves with the same P3 latencies, regardless of whether the stimulus was a target or nontarget. Thus, the major ERP aberrations manifested by alcoholics are (1) lack of differentiation between their responses to relevant and irrelevant inputs and (2) the low voltages of their event-related activity. These aberrations suggest underlying brain dysfunction that impairs sensory-filtering and probability-matching processes.

The finding of reduced P3 amplitudes in alcoholics in visual oddball paradigms has been replicated in our own laboratory, as well as in other laboratories (Emmerson et al., 1987; Patterson et al., 1987; Pfefferbaum et al., 1991; Porjesz et al., 1987a). Using another visual oddball P3 paradigm, (Porjesz et al., 1987a) we were interested in determining the effect of difficulty of discrimination on the amplitude of P3 in alcoholics. P3 components were obtained to two targets—an easy-to-discriminate target that was 90° from the vertical nontarget and a target that was difficult to discriminate (only 3° from the vertical nontarget). Once again, we found that alcoholics manifested significantly decreased P3 amplitudes. This diminished amplitude was even more apparent for the easy 90° target than the difficult 3° target, as controls manifested extremely large voltages to the 90° targets. Furthermore, the amplitude of P3 was significantly larger to the 90° target than the 3° target in controls, but not in alcoholics. A larger P3 amplitude to the 90° target is predicted by many ERP studies in the ERP literature that have demonstrated that the more deviant a rare stimulus is from the background (the more easily discriminable it is), the larger the P3 amplitude (Ford et al., 1979; Johnson and Donchin, 1978; Ritter et al., 1972; Ruchkin and Sutton, 1978; Towey et al., 1980). Perhaps the lack of P3 amplitude difference in the alcoholic group on the basis of ease or difficulty of discrimination indicates that they are more uncertain of the correctness of their decision than are controls, as they seem to stress speed over accuracy. (Their reaction times (RTs) were faster, and they made more errors than controls.) In addition to the lack of differentiation in P3 amplitude between the two target stimuli, in contrast to controls, alcoholics did not even manifest significant differences in P3 amplitude between target and nontarget stimuli. (This paradigm is more likely to elicit a P3-like component to nontargets as they are so similar to the difficult-to-discriminate targets, which are only 3° from vertical; therefore each nontarget is viewed as a potential difficult target.)

Using a visual oddball task, Emmerson et al. (1987) found that only the peak-to peak amplitude of N2-P3 differentiated alcoholics from nonalcoholics. To rule out age effects, they only examined alcoholics who were younger than 40. Furthermore, they studied alcoholics who were abstinent at least 1 month to rule out alcohol and withdrawal effects. Similarly, both Patterson et al. (1987) and Pfefferbaum et al. (1991) reported decreased P3 amplitudes to visual target stimuli in oddball tasks in the absence of latency delays.

Thus, it seems that all visual oddball studies in alcoholics concur that alcoholics manifest reduced P3 amplitudes to attended target stimuli. This finding seems to be very robust as it has been replicated across many different laboratories using numerous visual oddball paradigms.

In addition to standard oddball paradigms, other visual P3 paradigms elicit diminished P3 amplitudes in alcoholics. Using a Go/No-Go visual paradigm, Pfefferbaum et al. (1987) reported lower P3 amplitudes in alcoholics under Go, but not No-Go conditions. In addition, the scalp distribution was flatter for alcoholics for the Go and not the No-Go condition. Ciesielski et al. (1985) reported lower peak-to-peak N2-P3 amplitudes with a visual memory paradigm and different hemispheric latency distributions between alcoholics and controls.

In another visual P3 paradigm involving incentive factors, Porjesz et al. (1987b) reported lower P3 amplitudes without latency delays to equiprobable high-incentive stimuli in alcoholics than in controls. Latency corrected average procedures indicated that these results were not due to latency jitter in the average, but rather to lower single trial voltages. This result was recently replicated by Pfefferbaum et al. (1991) in both visual and auditory oddball paradigms.

The relationship between visual P3 amplitude and structural brain damage as assessed with CT scans was investigated in our laboratory using the geometric shape paradigm described above (Begleiter et al., 1980b). Two groups of alcoholics were studied: those exhibiting severely widened cortical sulci (Pos-CT) and those who did not manifest enlarged cortical sulci (Neg-CT). The two groups did not differ in terms of age, education, and duration or amount of alcohol consumption. Alcoholics in the Pos-CT group manifested significantly lower P3 amplitudes to target stimuli than alcoholics without evidence of widened cortical sulci (Neg-CT). Both groups of alcoholics displayed significantly smaller P3 amplitudes to targets than control subjects. Neocortical shrinkage alone cannot expain the results of diminished P3 amplitudes in alcoholics, as both alcoholics with and without overt signs of cortical atrophy 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 contribute to the scalp P3. As it is well known that alcoholics manifest frontal

lobe damage, the reduced P3 amplitudes in alcoholics may be a manifestation of frontal damage in alcoholics.

The P3 results from auditory paradigms are not as consistent as those with visual paradigms. In an early auditory oddball study in which speed of reaction time was stressed, Pfefferbaum et al. (1979) reported no difference in P3 amplitudes between an older sample of alcoholics and healthy controls, but did report that alcoholics manifested delayed P3 latencies. In constrast, Patterson et al. (1987) reported decreased auditory and visual P3 amplitudes to target stimuli in the absence of latency delays in a bimodal study. In a subsequent identical study (Parsons et al., 1990), this group of investigators replicated their N1 and P3 findings in male but not female alcoholics. Similar findings of P3 amplitude decrements in the absence of latency delays to auditory target stimuli have been obtained in our laboratory (Cohen et al., 1995; Hertz et al., in press; Porjesz et al., 1988).

Pfefferbaum et al. (1991) has also recently reported that P3 amplitudes were significantly different between alcoholics and controls to attended target stimuli in both visual and auditory oddball paradigms. In agreement with the study by Porjesz et al. (1987b), single-trial latency adjustment procedures indicated that these amplitude differences were due primarily to signal size differences between the two groups and not to 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 over the average. Furthermore, standard deviations of single-trial P3 latencies indicated that there were no significant differences between groups for either the auditory or visual paradigm.

P3 latencies were only found to be delayed in alcoholics to attended auditory targets; this was not the case for attended visual targets or unattended rare auditory stimuli in the same subjects. This study helps clarify earlier differences in the literature regarding whether or not 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) report RT delays in alcoholics to auditory but not visual attended targets. However, Porjesz et al. (1987a) reported P3 latency delays in alcoholics in easy but not difficult discrimination tasks. Therefore, it is possible that, rather than being modality specific, P3 latency delays in alcoholics are only apparent to easy discriminations between targets and nontargets. Auditory oddball paradigms tend to be easier than visual paradigms. In the study of Porjesz et al. (1987a), although controls manifested significantly earlier P3 latencies to easy discrimination than to difficult discrimination, alcoholics did not manifest differences in P3 latency depending on task difficulty; in alcoholics the P3 latency delays to the easy targets were prolonged to latencies comparable to a difficult discrimination task. These results suggest that alcoholics, in contrast to controls, find both tasks difficult and adopt an undifferentiated mode of responding, regardless of task requirements.

Most studies examining the effects of alcoholism on the brain have focused exclusively on male alcoholics. This is partly due to the fact that until recently, the number of reported female alcoholics was low. However, with secular trends, the number of female alcoholics has been increasing and more recently, studies have begun to focus on female alcoholics. As previously discussed, Parsons et al. (1990) have reported that although male alcoholics manifest low P3 amplitudes, female alcoholics do not manifest any P3 amplitude differences from normal subjects. Another study conducted by Hill and Steinhauer (1993a) found that female alcoholics showed significant deficits in P3 amplitude compared to female controls and their unaffected female siblings. Similarly, findings from an ongoing national study (Consortium on the Genetics of Alcoholism; COGA) indicate that female alcoholic probands manifest decreased P3 amplitudes compared to controls, though not to the same extent as males (Porjesz et al., 1993). More investigations of female alcoholics are necessary to elucidate these differences.

Taken together, the most consistent electrophysiological measure that differentiates alcoholics from healthy controls is their decreased P3 amplitude to targets for visual tasks at the Pz electrode. Although these findings have also been reported in the auditory modality, they are not as robust. It should be noted that there is evidence indicating that the visual and auditory P3 are generated at different brain loci. Furthermore, many different kinds of P3 are elicited under different experimental conditions with different brain generators (Ruchkin et al., 1990). The P3 components discussed thus far are obtained to attended stimuli of significance, to which the subject is required to make some response. However, automatic paradigms in which the subject is not asked to attend to rare deviant stimuli also elicit a different P3 with a more frontal topography (P3a).

Although most attention has been focused on the attended P3b paradigms in which it is necessary that the subject attend to the target selection (control processes), a small number of studies have also been conducted to examine automatic processes in which the subject does not attend to the processing of rare stimuli. In an inattentive auditory oddball paradigm, Pfefferbaum et al. (1991) found that, although P3 amplitudes to rare unattended stimuli were smaller in alcoholics than controls, this result approached but did not reach significance. However, this study used a somewhat small sample size (23 alcoholics and 21 controls). Perhaps with a larger sample this would have reached significance.

Using an almost identical automatic auditory oddball paradigm in our laboratory, Realmuto et al. (1993) found that alcoholics manifested significantly lower P3 amplitudes than 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 lab 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 against a repetitive background. Both studies concur that there are not significant differences in midline topography (Fz, Cz, Pz) between the two groups in P3 amplitude to unattended rare stimuli at any

of the three midline sites. Furthermore, although Pfefferbaum's results were not significant, they are in the same direction as Realmuto's findings and almost reach significance. Taken together, these findings suggest that automatic match/mismatch processes are impaired in alcoholics, though not perhaps to the same extent as under attend conditions.

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

Taken together, it seems that alcoholics are unable to automatically distinguish deviant stimulli from repetitive background stimuli, suggesting that simple processes of template match/mismatch are impaired. 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. These results suggest deficits in both automatic and control processes in alcoholics.

N2 (MMN). Another component of the ERP that has been examined in alcoholics is the N2 component, a negative component that occurs approximately 200 milliseconds after the stimulus. 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 can be taken as an early accurate 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 a superior index of stimulus evaluation time than reaction time (RT), as it is not confounded by the motor response. Reaction time is a complex measure of speed of information processing, as it depends on the end product of stimulus evaluation, response selection and organization, and the motor response. Although there are reports in the literature of delayed RTs in alcoholics (Bertera and Parsons, 1973; Talland, 1963; Vivian et al., 1973), reaction time studies alone cannot ascertain which aspect(s) of this complex process are slowed in alcoholics.

We were interested in examining the speed of stimulus evaluation in alcoholics, using the latency of N2 as an index. We designed a visual-spatial ERP reaction time paradigm in which we could determine the relationship between difficulty of discrimination, N2 latency, P3 characteristics, and RT in alcoholics. The paradigm consisted of frequently occurring vertical lines (nontargets) and two kinds of rare targets; (1) easy-to-discriminate targets (90° deviant from vertical) and (2) difficult-to-discriminate targets (only 3° deviant from vertical). The subject was instructed to press a button as quickly as possible to all nonvertical stimuli.

As expected, the latency of N2 reflected the difficulty of discrimination in the healthy controls, being significantly prolonged for the difficult compared to the easy discriminations. In contrast, N2 latency did not reflect discrimination difficulty in the alcoholics, who manifested similar N2 latencies regardless of discrimination difficulty. Moreover, the N2 latency occurred significantly later in the

alcoholics than the controls for both the easy and difficult discriminations, suggesting that they find both discriminations more difficult and need more time for stimulus evaluation. The latency difference between groups was even more apparent for the easy discrimination than the difficult discrimination. These results imply that alcoholics need disproportionately more time to make an easy discrimination (vertical from horizontal) when compared to controls (who can discriminate very quickly) than to make a difficult discrimination (which both groups presumably find difficult).

Furthermore, the amplitude of N2 was larger for easy discriminations than for difficult discriminations in the controls, as would be expected, as the amplitude of N2 is related to the degree of stimulus deviance (Naatanen et al., 1980). The amplitude of N2 was the same in the alcoholics, regardless of discrimination difficulty.

There were no significant differences in RT between the two groups of subjects, although the alcoholics tended to have somewhat faster RTs than controls. However, the alcoholics tended to make more errors, both in terms of false alarms and missing target stimuli, although these results were not significant. This response pattern indicates that speed is stressed over accuracy (Kutas et al. 1977), implying that alcoholics adopt different response strategies than controls under these conditions. Furthermore, these findings 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 inattentive auditory oddball paradigm, Realmuto et al. (1993) found that controls exhibited larger N2 amplitudes than alcoholics at Fz and Cz, but not Pz. MMN amplitude was significantly different between groups, whereas its latency approached but did not reach statistical significance when age was parceled out (MMN latency was found to be 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 (under age 40) were accepted for the study (Emmerson et al., 1987), as well as in a visual oddball test-retest study (Glenn et al., 1993). Similarly, Hertz et al. (in press) found that the latency of N2 was prolonged in alcoholics to both attended targets and rare non targets in a modified auditory Hillyard paradigm in which the subject was required to attend to a rare tone in one ear.

An interesting recent study from Parson's group (Glenn et al., 1993) has reported that the latency of N2 predicts whether or not an alcoholic will resume drinking. At the initial testing, alcoholics who would later resume drinking manifested longer N2 latencies than those who did not resume drinking. This N2 measure was not affected by family history for alcoholism, as both the resumer and abstainer groups had an equal number of individuals with a family history of alcoholism. Perhaps whereas P3 amplitude is an index of family history of alcoholism, N2 latency represents resumer status. Furthermore, Grau et al. (1992) report that whereas P3 does not recover after 4 months of abstinence, N2 latency totally recovers. This is another indication that N2 latency may be related to drinking status.

Taken together, these data seem to indicate that alcoholics manifest prolonged N2 latencies (Emmerson et al. 1987; Glenn et al. 1993; Hertz et al. in press; Porjesz et al. 1987a). As N2 latency indexes discrimination difficulty, these prolongations in N2 suggest that alcoholics have more difficulty with stimulus evaluation than do healthy controls. As it is the resumers who manifest longer N2 latencies, perhaps they have even more impairment in the ability to evaluate and differentiate between stimuli. Thus, on the basis of both the N2 and P3 ERP component characteristics, it can be concluded that alcoholics have less efficient match/mismatch processes than controls and hence more difficulty evaluating the potential significance of a stimiulus.

N400. Another endogenous ERP component that has received a good deal of attention in the ERP literature is the N400 component, a late negative component with a maximum at the centroparietal scalp, occurring approximately 400 to 600 milliseconds after incongruous semantic stimuli. N400 has been found to vary with semantic incongruity, phonological priming or matching, and the extent of search in memory (see Kutas and Van Petten, 1988 for review).

In our laboratory, we recently completed a study examining the N400 component in alcoholics. The paradigm consisted of a lexical decision task requiring the subject to indicate as rapidly as possible whether a letter string is or is not a word. Words preceded by semantically related words are more quickly recognized as words than 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 similar fashion as to unprimed words; namely, in contrast to controls, they exhibit N400s to primed words. These impaired priming mechanisms suggest possible semantic memory deficits in alcoholics. This is the first time that semantic memory deficits have been demonstrated in alcoholics using electrophysiological measures.

Memory Potentials. To examine mnemonic processes that were not semantically mediated, we used a modified delayed matching-to-sample task, using stimuli that were difficult to name (Begleiter et al., 1993). Pairs of visual line stimuli (S1 and S2) that were either simple (consisting of a few line elements) or complex (consisting of a larger number of elements) were presented randomly. On half of the trials the test stimuli (S2) were identical to S1; on the other half of the trials S2 was distinctly different from S1. After each presentation of S2, the subject indicated if S2 matched S1 (choice RT). Accuracy and speed were emphasized equally.

In both alcoholics and control subjects, response times were significantly shorter for matching than for nonmatching stimuli for both simple and complex stimuli.

RTs were shorter for simple than complex stimuli. Although the results were similar in alcoholics, their RTs were longer than controls for all conditions.

The electrophysiological results from this paradigm indicate that, in normal subjects, a component occurring around 240 msec after the stimulus is related to object recognition, differentiating recognized from unrecognized stimuli; it is termed the visual memory potential (VMP); (Begleiter et al., 1993). The VMP is significantly larger to stimuli that differ from the previous stimulus (particularly for the easy condition) and is smaller to repetitive stimuli. This component seems to originate in the occipito-temporal area, an area known to be involved in visual memory, and is maximal at right temporal leads.

The latency of the VMP was earlier for matching than for nonmatching stimuli (recognition), with alcoholics manifesting later latencies than controls. The VMP yielded higher voltages to the nonmatching S2 than to the matching S2 in controls; however, alcoholics did not manifest any difference in neurophysiological characteristics between matches and nonmatches. This finding indicates that alcoholics cannot differentiate between stimuli they had previously seen from novel stimuli. Furthermore, the amplitude of the VMP to the nonmatching S2 was significantly different between alcoholics and controls, indicating that mismatch processes are impaired in alcoholics and suggesting memory deficits in this population.

On the basis of this memory study, it seems that alcoholics manifest difficulty in matching-to-sample processes. Their responses to nonmatching stimuli seem aberrant in that they are of lower voltage and are not differentiated from responses to matching stimuli. The data show that ERPs are different to a test stimulus, depending on whether or not it matches an immediately preceding sample stimulus in healthy individuals. This difference was most striking for the VMP component, which was significantly increased to novel, unfamiliar stimuli compared to previously observed, familiar stimuli in controls but not in alcoholics, suggesting visual memory impairment in alcoholics.

Taken together, the results from the P3, N2, N400, and visual memory potential (VMP) components of the ERP indicate that match/mismatch processes are impaired in alcoholics and suggest memory dysfunction. Alcoholics are deficient not only in their response to task-relevant target stimuli (P3b) but also to task-irrelevant rare stimuli (P3a). P3 deficits may be attributable to the malfunctioning of more rudimentary match/mismatch processes, in which the template is either lost or absent. These P3 results, coupled with those involving the delays in N2 latency, indicate that alcoholics have more difficulty with stimulus evaluation. Taken together, it seems that match/mismatch processes are less efficient in alcoholics, are less well localized, and take longer to occur. This suggests context updating and memory problems in alcoholics.

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

Thus, the memory dysfunction exhibited by alcoholics seems to be in terms of very rudimentary match/mismatch processes themselves, regardless of the type of stimuli, in both control and automatic conditions. It is most apparent under mismatch conditions, where healthy individuals manifest large electrophysiological responses (P3, MMN, VMP).

Recovery of Evoked Brain Potential Deficits with Abstinence

The EP is extremely sensitive to the various aspects of alcoholism: specifically, alcohol administration, withdrawal and long-term abstinence. Therefore, it is very difficult to determine whether the brain dysfunction manifested by alcoholics is the direct result of the time in the recovery process at which the recordings are obtained from alcoholics. Earlier EP studies of the recovery process in alcoholics investigated the first 3 or 4 weeks after detoxification and overlooked the effects of medication administered during treatment (e.g., Coger et al., 1976; Salamy et al., 1980). In these studies Antabuse (disulfiram) and/or Librium (chlordiazepoxide) were administered to recovering alcoholics, both of which affect EP voltages. Increased EP amplitudes have been reported in healthy 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.

A recent study of auditory EPs during withdrawal indicated that withdrawal was marked by increased N1-P2 components, particularly in seizure-prone alcoholics (Neiman et al., 1991; Noldy and Carlen, 1990). Similarly, Romani and Cosi (1989) report larger N1-P2 components and shorter P3 latencies in an auditory oddball paradigm during withdrawal in alcoholics.

In order to study whether EP aberrations manifested by alcoholics would recover 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 in the recovery process after the withdrawal period: at 3 to 4 weeks and again at 4 months. BAERs and auditory and visual P3s (in a bimodal paradigm) were recorded identically on both occasions. At initial testing we found that BAERs and conduction velocities were delayed. However, after 4 months of abstinence, alcoholics manifested improved BAER morphology, shortened latencies, and improved conduction times. These findings were replicated in Spain after a 1-year follow-up (Cadaveira et al., 1994).

The relative roles of abstinence from alcohol and nutritional factors in "recovery" still remain to be determined. Throughout the long-term abstinence program in our rehabilitation hospital, patients received extensive vitamin therapy and most likely improved their nutritional status. In addition, 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 brainstem latencies caused by aberrant fluidizing effects on the membranes, which 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).

As we were only able to examine reversibility in alcoholics who remained in treatment for the full 4 months and these alcoholics tended to be less impaired initially, we cannot be certain that recovery occurs in all alcoholics, regardless of the degree of impairment. It remains to be determined whether recovery occurs as a function of the initial degree of impairment, whether greater impairment requires longer time periods for reversibility, or whether recovery ceases beyond a certain critical level of impairment.

Despite the improvement in BAER with prolonged abstinence, there was no improvement in ERP morphology or P3 amplitude after 4 months of abstinence in the same alcoholics. The waveforms and decreased P3 voltages to both auditory and visual stimuli were strikingly similar at the initial test and retest. Furthermore, there was no improvement in the differential enhancement of P3 amplitudes on the basis of task relevance to target stimuli in these abstinent alcholics. These results suggest that the low P3 voltages may not be reversible, may precede alcoholism, or may recover more slowly after long abstinence periods. Evidence from our laboratory indicates that alcoholics still manifest low voltage P3 amplitudes even after extremely prolonged periods of sobriety (Porjesz and Begleiter, 1985). We examined nonhospitalized alcoholics who had been sober from 3 to 10 years with the same bimodal paradigm and found that they still exhibited low voltage P3 components. The same alcoholics exhibited normal BAERs. Thus, it seems that although some electrophysiological aberrations observed in alcoholics improve with prolonged abstinence, other electrophysiological anomalies do not change. The electrophysiological characteristics that do not recover with prolonged abstinence (P3) may in fact antecede the development of alcoholism and perhaps represent predisposing factors.

The test-retest reliability of ERP measures over a 14-month period in controls and alcoholics was also investigated by the Oklahoma group (Sinha et al., 1992). These investigators found that N1 and P3 amplitudes provided the most reliable measures in both groups, followed by N2 amplitude, N1 and N2 latency, and P3 latency. As male alcoholics manifest decreased visual N1 and P3 amplitudes and increased N2 and P3 latencies at Pz (Parsons et al., 1990; Patterson et al., 1987; Porjesz et al., 1987a), it is important to note that the test-retest reliability is the same for these groups.

Family History of Alcoholism and ERPs

It has generally been assumed that the brain abnormalities observed in alcoholics are due to the toxic effects of alcohol on the brain, nutritional deficits, or an

interaction of alcohol and nutritional-related factors. More recently, the evidence is amassing that some of these electrophysiological 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 generated in examining the meaning of the diminished P3 voltages observed in alcoholics. As the P3 component does not seem to recover with prolonged abstinence and its characteristics seem to be genetically determined (Polich and Burns, 1987), the effect of chronic alcohol abuse on P3 characteristics has come into question. Recently, a few studies have investigated 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, although the majority of alcoholics in our studies tend to have a family history of alcoholism, the groups of alcoholics are always composed of alcoholics with and without family histories of alcoholism. In one study in which we obtained a significant difference in P3 amplitude between alcoholics and controls, (Porjesz et al., 1987a), we divided the alcoholics into those with family histories of alcoholism and those without family histories. We found that the family-history-positive alcoholics manifested lower visual P3 amplitudes than alcoholics without family histories of alcoholism, but these results did not reach significance (Henry et al., unpublished data). However, they were based on small sample sizes. Patterson et al. (1987) reported significantly smaller auditory and visual P3 amplitudes in alcoholic males compared to controls. In addition, they found that alcoholics with family histories of alcoholism manifested the lowest P3 amplitudes; P3 differences between alcoholics with and without family histories of alcoholism were significant in the visual but not auditory modality, although they approached significance in the auditory modality as well. Patterson et al. (1987) attribute their P3 results to a family history of alcoholism. However, they did not tease out the 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 his colleagues (1991) indicates that, indeed, a family history of alcoholism rather than lifetime alcohol consumption determines whether alcoholics manifest low P3 amplitudes. 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 family-history-positive alcoholics.

Taken together, there seems to be sufficient evidence that reduced P3 amplitudes observed in alcoholics are more a function of family history than of chronic alcohol ingestion. Earlier differences between laboratories P3 results may in part be due to differences in the alcoholic samples in terms of family history of al-

coholism. Although other ERP component differences in alcoholics (e.g., BAER) reverse with prolonged abstinence, reduced P3 amplitudes do not (Porjesz and Begleiter, 1985). Furthermore, the recent findings of a PATH analysis conducted by Pfefferbaum et al. (1991), indicating that family history rather than drinking history determines the amplitude of P3, suggests that it is a trait measure that may be highly useful as a phenotypic marker for alcoholism. However, the studies reviewed thus far have dealt with EPs in alcoholics, where it is difficult to separate the consequences of years of chronic alcohol abuse from underlying factors. Therefore, a more direct approach to investigating the etiology of brain abnormalities in alcoholics is to look at individuals at risk who have not abused alcohol.

Offspring of Alcoholics

ERP Studies in Young, High-Risk Males. 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), 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 and Guze, 1974; Goodwin et al., 1973). 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 have been reported to be highly concordant among identical twins (Jonsson and Nilsson 1968; Loehlin, 1972; Partanen et al., 1966). Taken together, these population genetic studies 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 genetically determined. The production of fast EEG activity has been demonstrated to be genetically transmitted (Propping, 1977; Vogel, 1970; Young et al., 1972). In various studies, Vogel has reported on the hereditary nature of several EEG variants—monomorphic alpha, low-voltage EEG, EEG with alpha and beta diffusely mixed, EEG with fronto-precentral beta (Vogel, 1970; Vogel et al., 1986). They maintain 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 EPs are under genetic control. Monozygotic twins manifest EP 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 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) and fraternal twins (O'Connor et al., 1994). The heritibility of P3 amplitude has recently been reported to be high in two

separate studies. In an ongoing large national family study, the Consortium on the Genetics of Alcoholism (COGA), a preliminary segregation analysis of visual P3 amplitude in 243 individuals from 58 families, indicated the P3 heritability to be 0.59; the same findings were reported for auditory P3 amplitude in a twin study (O'Connor et al., 1994).

It is quite likely that a genetic predisposition to alcoholism is manifested in brain function, and it is possible that electrophysiological events may serve as biological markers. Therefore, investigating these genetically determined electrophysiological measures of brain function is an important approach to the study of possible genetic factors in alcoholism. The identification of genetically transmitted biological marker(s) would provide more definitive evidence that the etiology of alcoholism involves genetic factors. In addition, it could perhaps elucidate the potential nature of these genetic factors.

For over a decade, our laboratory has been studying ERPs in subjects at risk for alcoholism. In our first study, the high-risk (HR) group consisted of sons of alcoholic fathers between the ages of 7 to 13 who had no prior exposure to alcohol (Begleiter et al., 1984). Their fathers had been diagnosed with alcoholism (according to DSM-III-R) and had been in treatment for alcoholism at some time. Boys whose mothers either ingested alcohol during pregnancy or who drank excessively after birth were excluded. Only boys with neither medical problems nor exposure to alcohol or other substances of abuse were included in this study. The low-risk (LR) group consisted of healthy normal boys matched for age and socioeconomic status to the HR subjects. They were included only if they had no prior exposure to alcohol or other substances of abuse and if they had no first- or second- degree relatives with a history of alcoholism or other psychiatric disorder. With the exception of family history of alcoholism, the same exclusion criteria were used in both the LR and HR groups.

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 microswitches to the targets, as quickly and accurately as possible, indicating whether the right or left ear was presented. In the "easy condition," the head was facing forward (nose up on 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 than in the LR groups to all target stimuli. This group difference was most significant 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 high- and low-risk groups.

This study was the first in the field to indicate that P3 amplitude is significantly reduced in boys at risk for alcoholism, without exposure to alcohol. Since this

original study, several laboratories including our own have replicated these findings. O'Connor et al. (1986) replicated the findings of Begleiter et al. (1984) using the identical head orientation paradigm; specifically, they reported reduced P3 amplitudes without the administration of alcohol in an older group of high-risk males. More recently, Hill and Steinhauer (1993b) have replicated these findings with the same paradigm in prepubescent boys at risk for alcoholism.

Begleiter et al. (1987b) studied another group of sons of alcoholics to determine whether the reduced P3 amplitudes observed in high-risk subjects was modality or task specific. A modified auditory oddball task was used, in which subjects pressed a button in response to rarely occurring tones presented at a random rate; accuracy was stressed over speed. Twenty-three matched pairs of family-history-positive (FHP) and family-history-negative (FHN) males between the ages of 7 to 16 were studied; they were carefully interviewed to ascertain that they had no exposure to alcohol or illicit drugs. The fathers of high-risk boys in this sample met the criteria for male-limited (type 2) alcoholism (Cloninger 1987). They manifested early-onset alcoholism, had a high rate of recidivism often accompanied by petty criminality, and required extensive treatment. Additionally, the high-risk boys came from families in which there was a dense history of alcoholism. As in the previous visual study, the FHP boys manifested reduced P3 amplitudes. The reduced P3 voltages in HR males in this auditory paradigm suggest that these reduced P3 voltages are not task or modality specific; they seem to be present in auditory and visual paradigms under conditions of speed and accuracy.

Another laboratory (Whipple et al., 1988, 1991) used a continuous performance test (CPT) to examine ERPs in prepubescent boys at high risk for alcoholism. 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 identity of a 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, 1987b) and O'Connor et al. (1986, 1987), Whipple et al. (1988) report a reduction in the amplitude of the late positive complex (LPC), including a P3 component. Later studies in the same laboratory replicate these original findings (Berman et al., 1993; Noble, 1990; Whipple et al., 1991).

An interesting study by Berman et al. (1993) indicates that P3 amplitude in prepubescent boys predicts later substance abuse in adolescence. Four years after the initial electrophysiological testing, these adolescents were administered a substance abuse questionnaire dealing with alcohol and drug use. P3 amplitudes of the lowest voltage at initial test (prepubescent) were associated with the highest substance use scores. These exciting findings provide strong evidence that P3 amplitude in prepubescent boys may provide a vulnerability marker for the development of later substance abuse disorders.

In our own laboratory we have recently replicated our original findings of reduced visual P3 voltages without the administration of alcohol in an older sample (ages 18 to 23) of sons of male alcoholics (Porjesz and Begleiter, 1990). The sample consisted of 25 male offspring of carefully diagnosed (DSM-IIIR/RDC)

male alcoholics and was selected from high-density alcoholic families (mean number of alcoholic family members = 4), excluding cases where alcoholism may have been sporadic. 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. They were selected from families in which there was no history of alcohol abuse or alcoholism in any first- or second-degree relatives. Family-history-positive and negative subjects were carefully matched on drinking history, including duration and quantity-frequency information.

We used another visual-spatial paradigm involving easy and difficult line discriminations, a paradigm that had previously elicited low-voltage P3 amplitudes in abstinent alcoholics (see the section on P3 in alcoholics for a description of the paradigm and results). The stimuli consisted of a nontarget (vertical line) and two targets: an easy target that deviated from vertical by 90° (horizontal line) and a difficult target that deviated from vertical by only 3°. The subject pressed a button as quickly as possible (RT) to all nonvertical stimuli.

The results indicated that, before alcohol ingestion, P3 amplitude was significantly lower in HR subjects compared to controls. This replicates our previous findings (Begleiter et al., 1984, 1987b) of lower-voltage P3s in an older sample of high-risk males, as well as those of O'Connor et al. (1986, 1987) and Whipple et al. (1988, 1991). The largest differences in P3 amplitude between groups occurred to the easy target, to which LR subjects manifested extremely high voltages. These results are the same as those we obtained in alcoholics with the same paradigm where the easy target elicited the greatest significant difference in P3 amplitude between groups (Porjesz et al., 1987a). This P3 amplitude difference between groups was most apparent at Pz and Cz electrodes.

Most recently in another auditory target selection task, we observed that adolescent HR males manifest lower amplitude P3s than LR males. In this paradigm, modified after Hillyard et al. (1978), rare or frequent tones were randomly presented rather quickly (600–800 msec) to either the right or left ear. The rare tones to a specific ear are designated as targets, and the subject presses a button in response as quickly as possible. The same rare tones to the other ear are ignored.

In the absence of other differences between groups (N1 amplitude), HR males manifested lower amplitude P3 components to both the rare attended (P3b) and unattended (P3a) tones. These findings indicate that HR subjects do not make probability matches as well as controls. In an inattention auditory oddball paradigm, we have also found that P3a is of lower amplitude in HR adolescent males. In this experimental design, subjects read a book while rare and frequent tones are randomly presented binaurally via headphones.

Most studies dealing with electrophysiological measures in subjects at risk for alcoholism have focused on males only. Recently Hill and Steinhauer (1993b) studied the P3 responses to a visual discrimination task of both male and female pre- and postpubertal subjects at risk for alcoholism. The task they used was identical to the one designed by Begleiter et al. (1984), consisting of heads rotated

in various positions (see description above). They replicated the P3 amplitude findings of Begleiter et al. (1984) in the prepubescent boys. However, they did not find that pre- or postpubescent females manifested lower P3 amplitudes, nor did postpubescent males.

Taken together, these studies examining P3 amplitude indicate they are reduced in voltage in older and younger high-risk males both to attended and unattended stimuli and to easy and difficult discriminations in visual and auditory modalities. A recent meta-analysis (Polich et al., 1994) of all the research on P3 characteristics in subjects at risk indicates that although there is a general consensus that P3 amplitude is of lower voltage in subjects at risk for alcoholism, it is most likely to be observed in young prepubescent males using difficult visual tasks. There seem to be more variable results in older offspring, particularly with auditory easy tasks. Despite the general consensus that P3 amplitudes are of lower voltage in high-risk males, some studies have failed to replicate these findings. Polich and Bloom (1987, 1988) and Baribeau et al. (1987) have not observed significantly reduced P3 amplitudes in the sons of alcoholics.

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

Although high-risk subjects did not exhibit reduced P3 amplitudes, the light drinkers manifested insignificantly 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 lower P3 amplitude in the unattended channel would reach significance with a larger number of subjects. As mentioned previously, we have found reduced P3 amplitudes to rare tones in the unattended channel in HR subjects with a similar Hillyard paradigm as the one described by Baribeau et al. (1987).

High-risk subjects manifested significantly larger N100 components than low-risk subjects in the attention condition; this finding perhaps indicates that the high-risk subjects in their study paid more attention than the low-risk subjects to the stimuli. Furthermore, it is possible that the high-risk subjects find the tone discrimination task more difficult than the LR group (500 Hz versus 600 Hz) and hence needed to pay more attention.

Finally, it seems that the subject sample represents an older group of "high-risk" individuals. There is a rather large age range (19-35), with mean ages of 27 (high risk—heavy drinking), 22 (high risk—light drinking), 24 (low risk—heavy drinking), and 25 (low risk—light drinking). It seems that these high-risk subjects may have passed the age of risk, and perhaps the sample is not representative of a group at high risk for alcoholism, considering that 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, and this represents a skewed sample of high-risk subjects, perhaps endowed with protective mechanisms. Certainly, their larger N100 component suggests they are atypical. In a P3 study by Hill et al. (1988), increased cognitive efficiency in nonaffected siblings of alcoholics was reported. They observed shorter P3 latencies in these nonaffected siblings and suggest that this offers protection against the development of alcoholism.

San Diego Studies in High-Risk College Students. In various studies in San Diego examining ERPs in college students with positive family histories of alcoholism, conflicting ERP results have been reported. These studies are mostly the work of Neville (Elmasian et al., 1982; Neville and Schmidt, 1985; Schmidt and Neville, 1985) and Polich (Polich and Bloom, 1986, 1987, 1988; Polich et al., 1988; Schuckit et al., 1988).

After the administration of either alcohol or a placebo, differences in P3 characteristics have been found between subjects at high and low risk for alcoholism. Elmasian et al. (1982) studied the P3 and slow-wave components of the ERP in high- and low-risk male college students (ages 20 to 25) under placebo, low dose, and high doses of alcohol. After alcohol or placebo administration, they reported significant P3 amplitude decreases in the high-risk compared to the low-risk 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 high-risk subjects. Unfortunately, different sets of subjects were used for each dose, and there were only five pairs of subjects per group, making it difficult to interpret the data.

In a subsequent study in the same laboratory (Neville and Schmidt, 1985) the late positive component (LPC) of the ERP in high-risk 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 observed between groups.

In another study, Schmidt and Neville (1985) investigated ERPs in high-risk males while they were engaged in a visual language task. They found that the N430 component (the component related to semantic processing) was significantly smaller in men at high risk for alcoholism than in men at low risk. Moreover, in the high-risk 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 is affected by a family history of alcoholism and that there is an interaction between family history and alcohol consumed per occasion and N430. We are currently examining high-risk 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 male college students with and without family histories of alcoholism. Using an auditory oddball paradigm, Schuckit et

al. (1988) did not find any ERP differences betwen FHP and FHN subjects before ethanol ingestion or after a placebo dose. After a high dose of ethanol (1.1mL/kg), P3 latency delays returned to baseline measures more rapidly in FHP men. This intriguing finding suggests that some electrophysiological differences between FHP and FHN individuals are apparent only in response to ethanol challenges, perhaps representing tolerance in the FHP subjects that may be innate.

The initial placebo effect in FHP subjects (Elmasian et al., 1982) was not replicated in the same laboratory (Polich and Bloom, 1988). These ERP results may be spurious as they involve very small sample sizes. Elmasian et al. (1982) tested only five subjects per group, and Polich and Bloom (1988) tested only ten subjects per group.

An inverse correlation between the amount of alcohol consumption (drinks per sitting) and the amplitude of P3 was found by Polich and Bloom (1987) without the administration of alcohol. However, this relationship was only apparent for a difficult discrimination task in FHP subjects. Although there was a trend in this direction in FHN subjects, it was not significant. The authors concluded that FHP subjects are more sensitive to the effects of alcohol than are FHN subjects. When a similar intensity discrimination study was performed in the visual modality, no correlation betweeen P3 characteristics and the amount of alcohol typically consumed was found (Polich et al., 1988). Futhermore, in yet another study designed to replicate the findings of Elmasian et al. (1982), Polich and Bloom (1988) not only did not replicate their previous findings of a placebo effect in the FHP group but also now reported that in both FHP and FHN subjects there was a correlation between P3 latency and the amount of alcohol consumption.

Thus, these findings relating alcohol consumption to P3 characteristics do not seem robust. In the same laboratory, using samples drawn from the same basic population of students, their findings are not readily replicable. Previous alcohol consumption has been found to correlate with P3 amplitude only, particularly in FHP subjects (Polich and Bloom, 1987), to correlate with P3 latency only (Polich and Bloom, 1988), and to be uncorrelated with any previous drinking variables (Polich et al., 1988). The relationship between P3 characteristics and drinking history is as yet an unresolved issue in other laboratories as well. O'Connor et al. (1986) report no relationship between any P3 characteristic and drinking history, whereas Steinhauer et al. (1987) report a correlation between drinking history and P3 latency. In addition to correlations between P3 characteristics and drinking history, as mentioned previously, N430 latency has been reported to correlate with the number of drinks per occasion in HR subjects (Schmidt and Neville 1985).

Two possible explanations for the lack of results in the San Diego group are the mode of assessment of alcoholism in the fathers and the clinical assessment of their families in general. A questionnaire was filled out by the son about his father's alcohol and psychiatric history and that of his first- and second- degree relatives, and a single positive symptom regarding the father's alcoholism was required to qualify. Thus, it is possible that in a large percentage of subjects, the offspring are not offspring of alcoholics, but of heavy or moderate drinkers. This

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 high-risk subjects without the ingestion of alcohol in four different paradigms thus far; (1) a compex visual response-compatibility/incompatibility design (Begleiter et al., 1984), (2) an auditory modified oddball paradigm (Begleiter et al., 1987b), (3) a visual discrimination paradigm (Porjesz and Begleiter, 1990), and (4) an auditory Hillyard paradigm (Porjesz and Begleiter, unpublished data). However, 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, whereas response selection difficulty does not.

ERP Studies with Alcoholization in High-Risk Subjects. More recently, we 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 (aged 19 to 24) received either a placebo or one of two ethanol doses (0.5 mL/kg and 0.8 mL/kg) mixed with three parts ginger ale on three separate occasions. A visual ERP paradigm involving easy and difficult line orientation discriminations was utilized (see the section on P3 in alcoholics for a description). ERPs and measures of levels of intoxication were obtained pre-ethanol and at 20, 60, 90, and 130 minutes after ethanol ingestion. Blood alcohol levels (BALs) were monitored at 10-minute intervals throughout the test session. No significant differences were obtained between groups in terms of BALs or intoxication ratings.

As indicated previously, before alcohol ingestion, the amplitude of P3 was significantly smaller in the HR compared to the LR group to all target stimuli, particularly the easy target. Alcohol ingestion did not affect the difference in amplitude between groups. Although there was a tendency for alcohol to depress the amplitude of P3 after alcohol ingestion in both groups, this did not reach statistical significance. However, during the ascending phase of the blood alcohol curve, the high-risk group manifested a larger percent decrement in P3 amplitude than the low-risk group to both target stimuli. This finding perhaps indicates greater sensitization in the HR group on the ascending phase of the BAL (Newlin and Thompson, 1990). We have obtained similar findings with slow alpha EEG in our laboratory (Cohen et al., 1993), where we found more of an increase in slow alpha activity in the high-risk subjects after an alcohol challenge.

No significant difference in the latency of P3 occurred between groups before alcohol ingestion. The latency of P3 occurred significantly later to the difficult discrimination target than to the easy target in both groups of subjects. The high

dose of alcohol significantly increased the latency of P3 to the difficult target in both groups of subjects at all but occipital electrodes. This effect was maximal between 60 to 90 minutes post ethanol; namely, at peak and early descending blood alcohol levels. Although the HR and LR groups did not differ significantly in terms of initial alcohol-induced P3 latency delays, the HR group tended to recover more quickly to prealcohol ranges. However, they remained delayed in the LR group throughout the study (130 minutes postalcohol). This replicates the findings of Schuckit et al. (1988), who reported that family-history-positive males recover more quickly from P3 latency delays induced by alcohol.

The N1 amplitude was significantly decreased by alcohol ingestion beginning at 20 minutes, particularly for the nontarget stimulus at occipital leads. This result was more pronounced in the LR than the HR group. Although N1 amplitude to nontargets remained depressed in the LR group throughout the test session, it recovered in amplitude by 90 minutes in the HR group. These results suggest that the high-risk subjects exhibited more innate tolerance to alcohol than the low-risk group. The N1 amplitude did not decrease to the difficult target and was somewhat decreased to the easy target by alcohol. These results support the finding by Roth et al. (1977) that attentional factors can counteract the N1 decreases caused by alcohol and Campbell's (Campbell and Lowick, 1987) finding that the largest alcohol effects are obtained when attention is mobilized least (to nontargets). The differential effect of alcohol on N1 is an important difference between the two groups in the way they respond to an ethanol challenge and is similar to the behavioral results reported by Schuckit (1980, 1984, 1988). These results suggest that the high-risk subjects exhibit more acute tolerance to alcohol than the low-risk group. Although there was a tendency for the subjects in the HR group to drink more frequently than the low-risk subjects and to consume more alcohol per sitting, neither of these measures reached statistical significance. However, at the present time we cannot conclude whether this N1 effect is due to innate or acquired tolerance. It was concluded that ERPs provide sensitive indices of state and trait variables involved in alcohol consumption and that different ERP characteristics are sensitive to different aspects of this multi-faceted problem. It remains for future research to determine whether those individuals with low P3 amplitude prior to alcohol ingestion manifest less N1 responses to alcohol and whether these individuals are in fact at higher risk for alcoholism.

To differentiate those aspects of electrophysiological function that antecede alcoholism from those that are the consequence of years of heavy drinking, we have investigated in the sons of alcoholics many different EP characteristics that are aberrant in alcoholics. In one study (Begleiter et al., 1987a), we examined BAERs in sons of alcoholic fathers, as we had previously found brainstem anomalies in alcoholics (Begleiter et al., 1981). We tested 23 sons of alcoholics (7 to 13 years of age) and 23 matched controls. In contrast with our P3 findings, we did not observe any significant differences in BAER measures between high- and low-risk subjects. This finding indicates that the BAER abnormalities observed in alcoholics are a function of alcoholism, whereas the P3 amplitude differences are

independent of alcohol effects and represent trait characteristics. This finding is further underscored by the recovery of BAER but not P3 abnormalities with prolonged abstinence. We are currently examining other ERP components that are aberrant in alcoholics (e.g., MMN, P3a, N400, and VMP) in subjects at risk for alcoholism to determine whether they antecede alcoholism or are the consequence of drinking.

The lack of consensus of results among laboratories can 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 an 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 "high-risk" subjects in some studies may include offspring of heavy drinkers or problem drinkers. This inclusion weakens the loading of familial alcoholism, making it less likely to obtain significant results between groups. Such problems as co-morbidity for other psychiatric problems are also treated differently in different studies; individuals manifesting co-morbid psychiatric diagnoses (e.g., anti-social personality or affective disorder) may be excluded from some studies and included in others.

As alcoholism is a heterogeneous disease, high-risk groups in different studies may comprise different numbers of offspring of different types of alcoholism, e.g., type 1 and type 2. Various types of prealcoholics may manifest different electrophysiological patterns before and after alcohol administration. That alcoholism is a clinically heterogeneous disease with possible genetic heterogeneity is underscored by the fact that different studies often yield inconsistent results. Often the "high-risk" subjects studied are beyond the age of risk, or the stringent screening criteria rule out potential pre-alcoholics. Furthermore, environmental influences must be taken into account; such variables as socioeconomic status, education, and age may affect the results obtained. Additionally, differences in selection criteria for the control group may also determine whether differences between high- and low-risk groups will be found. Therefore, subject selection remains a major problem in "high-risk" research.

ERPs: State and/or Trait Markers for Alcoholism

Evoked potentials are sensitive to the various aspects of alcoholism; namely, alcohol administration, withdrawal, and long-term abstinence. In addition, some ERP characteristics seem to represent invariant electrophysiological signatures that are genetically determined. Therefore, ERPs provide sensitive indices of both state

and trait variables involved in alcohol consumption. Different ERP characteristics are sensitive to different aspects of this multifaceted issue.

The **amplitude of P3** distinguishes between alcoholics and healthy controls, as well as subjects at high and low risk for alcoholism. It is of lower voltage in alcoholics and in subjects at risk for alcoholism. These findings seem to be extremely robust, particularly for visual paradigms. In alcoholics, decrements in P3 amplitude do not recover after prolonged abstinence periods. P3 amplitude differences are apparent both before and after alcohol ingestion in high-risk nonalcoholics. Furthermore, reduced P3 amplitudes have been found to be related directly to a family history of alcoholism and not to lifetime alcohol consumption. In light of this divergent evidence, reduced P3 voltages seem to represent a trait variable. Recent findings of a PATH analysis indicate that family history rather than lifetime alcohol consumption accounts for low-voltage P3 amplitudes in alcoholics. It has been suggested that this low-voltage P3 represents a marker for a predisposition to alcoholism.

Although alcohol ingestion does somewhat decrease the amplitude of P3, this is not its main effect. The ERP component characteristics most sensitive to alcohol ingestion are the amplitude of N1 and the latency of P3. Alcohol ingestion does not affect the P3 amplitude difference between alcoholics and controls. However, the rate of change of P3 amplitude under ethanol during the ascending phase of the blood alcohol curve is steeper in high-risk subjects, suggesting increased acute sensitization in these individuals.

The **latency of P3** seems to be extremely sensitive to the effects of alcohol, particularly for difficult discriminations (3° target) in all subjects. This ERP measure indexes a slowing in stimulus evaluation time with alcohol ingestion and seems to be a state variable. Its rate of recovery during the descending phase of the blood alcohol curve is faster in high-risk subjects, suggesting tolerance.

Similarly, the **amplitude of N1** is very sensitive to alcohol effects and is markedly decreased after alcohol ingestion (state variable). The amplitude of N1 (Nd) has been found to discriminate between alcoholics and controls for visual tasks in the attended channel. These amplitude decrements resemble voltage levels obtained under the influence of alcohol. The N1 amplitude seems to distinguish between subjects at high and low risk for alcoholism after the alcohol challenge, but only under very specific conditions: less-attended stimuli at sensory sites. HR subjects recover pre-ethanol N1 amplitudes more rapidly than LR individuals.

Therefore, both N1 amplitude and P3 latency delays do not distinguish high-risk individuals from controls before the ingestion of alcohol. Yet, these measures change the most after alcohol challenges in all individuals (state dependent), and it is their rate of recovery that distinguishes between subjects at risk for alcoholism and controls. Individuals at risk for alcoholism recover from changes in these ERP measures to pre-ethanol levels more rapidly than controls, demonstrating greater tolerance. This may in fact shed light on the mechanism causing individuals at higher risk to drink greater amounts of alcohol, as the effect dissipates so rapidly.

Therefore, although P3 amplitude discriminates between alcoholics and subjects at risk for alcoholism from controls without the ingestion of alcohol, recovery of N1 amplitude depressions and P3 latency delays to preethanol levels seems to discriminate between them after alcohol ingestion.

Changes in BAER latency and conduction velocity seem to be sensitive to acute and chronic alcohol ingestion and hence are state dependent. Withdrawal is marked by shortened BAER latencies. Although abstinent alcoholics manifest delays in BAER and central conduction velocities, these delays seem to recover with prolonged abstinence. Furthermore, we failed to find BAER differences between subjects at high and low risk for alcoholism. These findings suggest that, in contrast to P3 deficits, abnormalities in BAER observed in alcoholics are due to the consequences of years of heavy alcohol abuse.

Thus, electrophysiological measures have an advantage over other techniques in that they can provide indices of both trait and state characteristics. These trait indices perhaps provide phenotypic markers (e.g., P3 amplitude, high-frequency beta) distinguishing subjects at risk for alcoholism without the administration of alcohol. The electrophysiological measures of state characteristics—how an individual's EEG and ERP respond to alcohol (e.g., changes in alpha and N1 amplitude)—also distinguish HR from LR groups, perhaps representing vulnerability markers for alcoholism. Furthermore, these electrophysiological measures may be useful in distinguishing different subgroups at risk for alcoholism. Future studies focusing on individual differences in electrophysiological measures before and after alcohol administration will help identify individuals at risk for specific types of alcoholism.

Summary and Conclusions

Several ERP components (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 and provides information on different facets of brain functioning: yet, it is with regard to an aspect that they share that alcoholics seem to be most impaired. The common denominator that underlies the electrophysiological impairment manifested by each of these components is impairment in basic match/mismatch processes, suggesting memory dysfunction.

On the basis of their ERP component characteristics, it is apparent that alcoholics do not differentiate electrophysiologically between relevant and irrelevant, target and nontarget, easy and difficult, primed and unprimed, familiar and unfamiliar, and even same and different stimuli. Indeed, they maintain the same ERP characteristics (both amplitude and latency), regardless of stimulus or task requirements. Alcoholics seem to adopt a mode of undifferentiated responding to all stimuli and tasks.

This finding perhaps indicates that in alcoholics their template for match/mismatch decisions is lost or not readily available. In either case it suggests a mem-

ory deficit where each incoming stimulus must be evaluated anew. Alcoholics manifest both types of brain dysfunction: the delay in N2 latency suggests that the template for comparison is not as readily accessible in alcoholics, whereas the low P3 voltages to targets (and low VMP amplitudes to nonmatching stimuli) suggest that, once retrieved, the match/mismatch processes themselves are impaired in alcoholics. As this impairment is manifested in both automatic (P3a) and control (P3b) processes, it suggests a malfunctioning of rudimentary probability-matching processes in which rare novel stimuli do not elicit responses different from those elicited by repetitive background stimuli. It is almost as though alcoholics are unable to utilize available information (e.g., template) to help them respond to incoming stimuli. This is also apparent in their responding to primed words as if they were unprimed (manifesting N400s); whereas normals utilize the priming information to facilitate their responses to primed words, alcoholics respond on the basis of each word de novo.

This memory deficit is most apparent in the processing of "different" (nonmatching) stimuli, to which the neural resources need to be mobilized most. In healthy individuals, the amplitude of P3 is directly related to the deviance of the target from the nontarget. However, in matching-to-sample paradigms, alcoholics respond to nonmatching S2 stimuli as if they were matching S2s, not producing the large voltages that normally accompany nonmatching stimulus responses. Similarly, in oddball paradigms, alcoholics manifest lower P3 voltages than controls to rare target (P3b) and nontarget stimuli (P3a) in a repetitive train. It is under conditions of easy discrimination (greatest deviance) that alcoholics manifest the greatest deficits in amplitudes when compared to controls. It remains to be determined whether the template for the familiar stimulus (nontargets, matches, primes) is not laid down in alcoholics or is lost, therefore not providing the background against which a different stimulus can be recognized, or whether alcoholics have difficulty retrieving the template, or both. In any case, alcoholics seem to have problems with the match/mismatch processes themselves and are unable to produce the voltages necessary for different or nonmatching stimuli (voltage production deficit).

As the neural origins of these ERP components are not known at the present time, it is difficult to determine which areas of brain damage are manifested by alcoholics. Increasing evidence indicates multiple contributions to scalp-recorded ERP components. It is tempting to speculate that what these components have in common is a frontal contribution, as frontal deficits have been reported in alcoholics on several neuropsychological tasks. As indicated in this review, there is evidence implicating frontal contributions to the P3 component. In addition, the mismatch negativity is thought to have contributions from frontal areas. Despite its origins in inferior temporal regions, recent evidence from our lab indicates some frontal contributions to the VMP component elicited in our matching-to-sample paradigm. Certainly, the match/mismatch processes themselves—namely, the ability to differentiate relevant from irrelevant, target from nontarget, matching from nonmatching stimuli—seems to be a frontal function.

Taken together, it can be concluded that alcoholics have less efficient match/mismatch processes, making it difficult for them to respond differentially to significant or novel stimuli. Alcoholics have difficulty evaluating the potential significance of a stimulus as their match/mismatch processes are impaired. This suggests memory dysfunction in alcoholics.

It remains for future research to separate those brain aberrations that antecede alcohol abuse from those that are the consequence of years of heavy drinking. The ability to utilize sophisticated neurophysiological tools to assess brain dysfunction in abstinent alcoholics and individuals at risk for alcoholism may prove most valuable in separating the deleterious effects of alcoholism on the CNS from the brain deficits that may antecede the development of alcoholism. The delineation of similar neurophysiological deficits in abstinent alcoholics and children at risk for alcoholism may be of fundamental importance in the identification of possible genetic marker(s).

Some electrophysiological measures yield similar ERP patterns in individuals at risk for alcoholism and in those observed in alcoholics. Specifically, the ERPs of sons of alcoholic fathers can be characterized by low-voltage P3 amplitudes. This robust finding has been replicated in many different laboratories with different experimental paradigms. As in alcoholics, this low-voltage P3 is particularly apparent in visual paradigms at Pz and Cz electrodes. The low P3 amplitude is apparent in high-risk subjects without exposure to alcohol. The reduced P3 voltages that have been reported in abstinent alcoholics have not been found to recover with prolonged abstinence. In contrast, BAERs seem to recover with prolonged abstinence in alcoholics and do not differ between high- and low-risk subjects (Begleiter et al., 1987a). Taken together, these findings suggest that P3 deficits observed in alcoholics and high-risk subjects antecede alcoholism, whereas BAER abnormalities in alcoholics are the consequence of alcoholism. Most importantly, a recent PATH analysis indicates that P3 amplitude decrements observed in alcoholics have been reported to be directly related to a family history of alcoholism and not to drinking history variables (Pfefferbaum et al., 1991). These exciting findings provide the missing link between P3 studies of alcoholics and subjects at risk for alcoholism, indicating that P3 characteristics are under genetic control and suggesting that low P3 voltages are trait rather than state characteristics in alcoholism.

There is substantial evidence indicating that electrophysiological characteristics (both EEG and ERP) are indeed under genetic control. The P3 component has been reported to be more similar among MZ twin pairs than among DZ twin pairs (O'Connor et al., 1994) and unrelated controls (Polich and Burns, 1987). The heritability of P3 amplitude has been reported to be 0.59 by O'Connor et al. (in press) in a twin study and in an ongoing national family study from the COGA project. In addition, ERPs have been reported to be similar in abstinent alcoholic fathers and their sons (Whipple et al., 1988). Thus, the reduced P3 voltage in high-risk subjects perhaps provides a phenotypic marker for alcoholism. However, although it remains to be determined with longitudinal studies whether those high-

risk individuals manifesting low P3 voltages are in fact those who go on to develop the disease of alcoholism, one recent study indicates that this is indeed the case. Berman et al. (1993) recently reported that low prepubescent P3 amplitudes predict later substance abuse disorders. We are currently in the process of determining the utility of P3 voltages as markers of alcoholism in our national COGA family study. Our preliminary results indicate that P3 amplitudes are lower in densely affected alcoholic families compared to control families. Among the prepubescent offspring of these densely affected families, there is a great deal of variability in their P3 amplitudes. It remains to be determined whether it is the young family members that manifest low P3 amplitudes who go on to develop substance abuse after they enter the age of risk.

Although high-risk individuals have also been reported to differ on other electrophysiological measures from controls (e.g., N2-P3a, MMN, and EEG), these findings have not yet been replicated across different laboratories and may not be as robust as the P3 findings. For example, although the EEGs of high-risk subjects have been reported to be characterized by excessive high frequency without the administration of alcohol, this has only been reported in one laboratory and has not been replicated even within the same laboratory. We are currently investigating other ERP components found to be aberrant in alcoholics (N400 and VMP) in subjects at risk for alcoholism to determine whether they antecede the development of alcoholism.

In addition to electrophysiological measures that differentiate high- from low-risk individuals without exposure to alcohol, other electrophysiological measures have been reported to differentiate individuals at risk with the use of alcohol challenges, e.g., changes in alpha, recovery from N1 amplitude reductions, and P3 latency delays of the ERP. Evidence is beginning to indicate which innate differences determine responsiveness to alcohol, including the predisposition to alcohol abuse. Genetic differences in strains of animals have been found to determine whether they are predisposed to drink alcohol or find it to be aversive (Rogers, 1972). Acute tolerance has been reported in preferrer (P) rats compared to nonpreferrers (NP) in terms of behavioral (Li et al., 1987; Lumeng et al., 1982, 1989) and autonomic measures (Froehlich et al., 1989). Furthermore, differences in neurophysiological responses to alcohol have been reported in different genetic rat strains (Sorenson et al., 1980). Humans have also been found to differ in their responsiveness to challenge doses of alcohol—augmenting/reducing (Buchsbaum and Ludwig, 1980; Spilker and Callaway 1969), family history for alcoholism (Cohen et al., 1993; Elmasian et al., 1982; Pollock et al., 1983; Porjesz and Begleiter, 1992; Schuckit et al., 1988) and flushers/nonflushers (Fukui et al., 1981). For example, findings in Japan indicate that "flushers" (who manifest an adverse flushing reaction to alcohol) are more susceptible to delayed BAERs than nonflushers when ingesting a challenge dose of alcohol (Fukui et al., 1981). It is possible that the low P3 amplitudes we observed in the young sons of alcoholics represent a vulnerability marker that may only become apparent in response to alcohol. Recent evidence indicates that sons of alcoholic fathers who manifest

abnormal P3 components before alcohol ingestion exhibit quicker recovery of both N1 amplitudes and delayed P3 latencies after alcohol ingestion, despite normal N1 amplitudes and P3 latencies prior to alcohol ingestion (Porjesz and Begleiter, 1992).

To determine whether these electrophysiological measures provide phenotypic markers of alcoholism, longitudinal studies will be needed to assess individuals as they pass through the age of risk. At present, there is no compelling evidence demonstrating that those individuals manifesting a low P3 amplitude are in fact destined to become alcoholics. Longitudinal studies of alcoholic and nonalcoholic families are underway to determine which family members become alcoholic as they pass through the age of risk. It is hoped that this approach will elucidate the link between measures of risk and development of alcoholism.

This chapter indicates that electrophysiological measures may serve as phenotypic markers for alcoholism. It does not suggest that these phenotypic markers are necessarily specific for alcoholism not that all individuals manifesting these markers will necessarily go on to abuse alcohol. However, there is evidence that individuals at risk for alcoholism (sons of alcoholic fathers) can be distinguished from those not at risk for alcoholism by electrophysiological measures, both without the ingestion of alcohol and in response to alcohol challenges. As these electrophysiological differences are genetically determined, the data imply that a predisposition or vulnerability to alcoholism is inherited. However, the role of environment and gene-environment interactions are not to be minimized in determining whether an individual manifesting this predisposition goes on to abuse alcohol.

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