Event-Related Potentials in Individuals at Risk for Alcoholism

B. PORJESZ AND H. BEGLEITER

Neurodynamics Laboratory, SUNY Health Science Center at Brooklyn, Brooklyn, NY 11203

FOR many years in our laboratory we have studied electrophysiological aberrations in abstinent alcoholics with the use of event-related potentials (ERPs) [for reviews see Porjesz and Begleiter (27,28)]. These ERP techniques require that the subject be actively engaged in a task—usually an information-processing task. The advantage of using ERPs to study brain function is that they combine cognition with electrophysiology. They can be recorded to attended and unattended stimuli.

We have focussed a great deal of attention on the P3 or P300 component, a positive component occurring between 300–500 msec after the stimulus. This is a prominent component related to stimulus significance, e.g., task relevance (33), unpredictability (6), infrequency (35) and motivational factors (1). We have reported that it is markedly reduced or absent in abstinent alcoholics (4, 26–30).

For many years we attributed this P3 deficit to the neurotoxic effects of prolonged chronic alcohol intake on the brain, nutritional deficits, or an interaction of alcohol and nutritional-related factors. More recently, we have found that while other ERP components recover with prolonged abstinence (e.g., Auditory Brainstem Potentials), P3s do not (28).

Population genetic studies have indicated that sons of alcoholics are four times more likely to become alcoholic than the sons of nonalcoholics (10,11), even when they are separated from their biological parents soon after birth. Studies of male adoptees in Scandinavia indicate that the biological rather than the adoptive parent is predictive of later drinking problems (5, 9, 10). Furthermore, the concordance rate of alcohol abuse between identical twins is almost double the rate for fraternal twins (16), and patterns of alcohol consumption have been reported to be highly concordant among identical twins (15, 17, 20). Taken together, these population genetic studies suggest that genetic factors may be involved predisposing sons of alcoholics to alcoholism.

It occurred to us that perhaps the P3 deficits we observed in abstinent alcoholics anteceded the development of chronic alcoholism and were possibly indicative of some predisposing factors. In order to test this hypothesis, Begleiter et al. (2) studied ERPs in sons of alcoholic fathers between the ages of 7–13 who had not had any previous alcohol exposure. The fathers of the high risk (HR) boys had received a DSM-III diagnosis of alcoholism and had been in treatment a long time; boys whose mothers drank alcohol during pregnancy or who drank excessively after birth, were excluded. We found that P3 amplitudes were significantly lower in this high risk group compared to matched control boys. We obtained this finding using a complex visual-spatial ERP design. This result has now been replicated in our own laboratory (3) as well as in several different laboratories (18, 19, 36) using different experimental paradigms.

Despite the general consensus that P3 amplitudes are of lower voltage in HR males, conflicting ERP results have been reported in various studies within the same laboratories at the University of California at San Diego (7, 21, 22, 24, 25). These investigators fail to replicate their own P3 results and also report conflicting findings about the relationship of P3 characteristics and previous alcohol consumption. It should be noted, however, that their sample consists of male college students with family histories of alcoholism or heavy drinking.

We undertook the present set of studies to see if we could replicate our P3 findings in an older group of young males. We were also interested in extending our findings to another visual-spatial P3 paradigm involving easy and difficult line orientation discriminations. We have previously demonstrated that abstinent alcoholics manifest lower P3 amplitudes with this design (12,29).

The data in the present report comes from a large ongoing study

1Requests for reprints should be addressed to B. Porjesz, Neurodynamics Laboratory, SUNY Health Science Center at Brooklyn, 450 Clarkson Avenue, Box 1203, Brooklyn, NY 11203.
in which we are looking at electrophysiological responses to three doses of alcohol in family history positive (FHP) and negative (FHN) subjects in many ERP paradigms as well as EEG. This paper will focus on the responses of both FHP and FHN subjects in a cognitive P3 design involving easy and difficult line orientation discriminations prior to the ingestion of alcohol.

METHOD

Subjects

The subjects were males between the ages of 19–24 (Table 1). All were “social” drinkers. They were recruited from various treatment facilities in New York City where their fathers were in treatment for alcoholism. Controls were either hospital employees or were recruited from newspaper ads. In both cases, a questionnaire dealing with alcohol, drug, medical and psychiatric histories of the subjects themselves and their first- and second-degree relatives was mailed and returned. This questionnaire served as a screening procedure for inclusion or exclusion to the next step of the study. On the basis of these questionnaire responses, subjects were contacted to take part in the study.

To be included in the FHP group, the potential subject had to have a definite alcohol-dependent father. This was equivalent to a DSM III-R diagnosis of alcohol dependence. In addition, we assessed the presence of alcoholism in any other first- or second-degree relatives. Individuals with mothers who abused ethanol were excluded. To be included in the FHN group subjects could not have any first- or second-degree alcoholic relatives. Subjects were excluded from both groups if they had major medical problems, were on any CNS-acting medication, had histories of psychiatric problems or had histories of IV drug use. Subjects were matched on age, education, marijuana use, weight, and cigarette use.

Upon arrival in the lab, subjects underwent an extensive psychiatric interview about drug and alcohol use, medical and psychiatric problems in themselves and in first- and second-degree relatives.

Experimental Procedure

Subjects were seated in a sound-attenuated chamber fixating on a point in the center of a computer CRT (44 cm away). They were presented with straight line stimuli (42 mm) rotated in 3 possible orientations, all passing through the central fixation point (visual angle 5.46°).

The stimuli were presented one at a time at a random rate (2–5 sec). The nontarget stimuli were frequently occurring vertical lines (75%). Two types of rarely occurring target stimuli were used: an easy discrimination, which differed from vertical by 90 degrees (horizontal line), and a difficult discrimination that differed from vertical by only 3 degrees. The targets were each presented 12.5% of the time.

The subject’s task was to press a button to all nonvertical stimuli as quickly as possible in a target selection, reaction-time paradigm.

Electrodes

The entire 10/20 system of electrodes was used (Electro-Cap), with the nasion serving as reference and the forehead as ground.

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>SUBJECT INFORMATION DESCRIBING FAMILY HISTORY POSITIVE (FHP) AND FAMILY HISTORY NEGATIVE (FHN) MALES USED IN THIS STUDY, IN TERMS OF AGE, SOCIOECONOMIC STATUS (SES), ALCOHOL INTAKE (FREQUENCY/MONTH AND NUMBER OF DRINKS PER OCCASION), FAMILY HISTORY OF ALCOHOLISM INCLUSION CRITERIA, NUMBER OF ALCOHOLIC FIRST- OR SECOND-DEGREE RELATIVES</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Subjects</th>
<th>FHN</th>
<th>FHP</th>
</tr>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Range</td>
<td>19–24</td>
</tr>
<tr>
<td>Mean</td>
<td>22.0±1.8</td>
<td>22.3±2.1</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>14.1±2.2</td>
<td>13.9±1.5</td>
</tr>
<tr>
<td><strong>SES</strong></td>
<td>Matched</td>
<td>Matched</td>
</tr>
<tr>
<td><strong>Frequency Alcohol Intake</strong></td>
<td>4.6 Days/Mo</td>
<td>5.1 Days/Mo</td>
</tr>
<tr>
<td><strong>No. Drinks/Occasion</strong></td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Family History of Alcoholism (DSM III-R)</strong></td>
<td>No 1st or 2nd Degree Alcoholic Relatives</td>
<td>Father Alcoholic Mother Nonalcohol Abuser plus Additional 1st and 2nd Degree Relatives</td>
</tr>
<tr>
<td><strong>Number of Alcoholic Relatives</strong></td>
<td>0.0</td>
<td>4.0</td>
</tr>
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</table>
Vertical and horizontal eye leads monitored possible eye movement contamination and trials with excessive eye movement (75 μV) were removed.

**ERPs**

The ERPs were amplified 20,000 times and were sampled for 100 msec preceding the stimulus (pre-stimulus baseline) and for 1000 msec following the stimulus every 5 msec (200 Hz sampling rate; bandwidth 0.1–100 Hz). On-line digital filtering was performed on the data between 0.1–30 Hz.

Data analyses were performed on the N1 and P3 components of the ERP which were measured baseline-peak.

**RESULTS**

The measures were subjected to a Repeated Measures Analysis of Variance (BMDP) and independent and dependent t-tests wherever appropriate (37). Degrees of freedom were reduced to 1 and N-1 according to the method outlined by Jennings and Wood (13) to take into account unequal variance-covariance matrices in repeated measure designs.

The data were analyzed separately for two separate identical occasions (baseline), prior to the ingestion of any liquid. On one occasion, the subjects drank a placebo after this baseline run; on the other occasion, they ingested ethanol after this run.

The results indicated that the P3 amplitude was significantly lower in the HR than the LR group (see Figs. 1–4). No significant differences in P3 latency were found between groups.

The mean amplitudes of P3 for the easy target in the LR and HR groups recorded at Pz on two separate identical occasions (baseline) are illustrated in Fig. 1. The mean P3 amplitude at Pz for the easy target is 19.01 μV (SD 7.71) in the LR group and 13.47 μV (SD 4.14) in the HR group on the placebo day; similarly the mean P3 amplitude is 19.77 μV (SD 8.67) and 12.97 μV (SD 4.87) for the LR and HR groups respectively for the same stimulus on the alcohol day. Individual t-tests indicated that the amplitude of P3 was significantly smaller in HR than the LR group at p<0.025 on both days.

Similar results were obtained for the difficult target (3°). Figure 2 illustrates the mean P3 amplitude for the 3° target in the HR and LR groups at Pz on the baseline runs.

The mean amplitude of P3 at Pz for the difficult target is 17.18 μV (SD 7.51) in the LR group and 12.67 μV (SD 6.97) in the HR group. The mean P3 amplitude for T3 is 17.46 μV (SD 8.75) and 12.74 μV (SD 3.06) for the LR group. The HR group P3 amplitudes were significantly lower than the LR group amplitudes at p<0.05 on both days.

Figure 3 illustrates the grand mean waveforms for the easy target in the HR and LR groups on both occasions. Figure 4 illustrates the grand mean waveforms for the difficult target in the HR and LR groups on both baseline runs.

**Reaction Time (RT)**

The reaction time (RT) data indicates that both groups of...
subjects responded faster to the easy discrimination than the difficult discrimination. In the LR group, the mean RT to the easy target is 603 (SD 85) and to the difficult target it is 627 (SD 84); for the HR group the mean RT is 646 (SD 85) for the easy target and 678 (SD 63) for the difficult target. The HR group responded significantly slower to both stimuli than the LR group.

**DISCUSSION**

The results indicate that the P3 amplitude is significantly lower in the HR subjects compared to controls prior to ethanol ingestion. This replicates our previous findings of lower voltage P3’s in an older sample of high risk males and those of O’Connor et al. (18,19) and Whipple et al. (36).

The largest difference 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 (29). This P3 amplitude difference between groups was most apparent at Pz and Cz electrodes.

The amplitude of P3 tends to be larger (and earlier) to easily discriminated targets. With increases in task difficulty, the amplitude of P3 decreases and its latency increases. In both groups of subjects, the amplitude of P3 was larger to the 90° than the 3° stimulus.

The larger P3 voltage to the 90° target is predicted on the basis of Ruchkin’s equivocation hypothesis (32), which states that the amplitude of P3 depends on the amount of information delivered by a stimulus minus the amount lost due to uncertainty (equivocation), or the amount ‘‘received.’’ Many studies have demonstrated that the more deviant a rare stimulus is from the background, the more easily discriminable it is (and hence the greater the certainty it has occurred), and the larger the P3 amplitude (8, 14, 31, 32, 34). The lower P3 amplitude in the high risk group for both stimuli perhaps signifies that it is a more difficult discrimination for the HR subjects. Perhaps they are more uncertain of the correctness of their decisions.

RT’s were significantly longer to the difficult than the easy target in both groups. However, the RT 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. The latency of P3 precedes the motor response and can be taken as more of an index of stimulus evaluation time than RT. The more difficult a discrimination, the later the P3 latency. This indeed was the case in both groups of subjects where P3 occurred later to the 3° target than the 90° target.

In conclusion, it seems that the amplitude of P3 distinguishes between subjects at high and low risk for alcoholism—being of lower voltage in subjects at risk for alcoholism. This is apparent prior to alcohol ingestion and seems to represent a trait variable. It has been suggested that this low voltage P3 represents a marker for a predisposition to alcoholism. Reduced P3 voltages have been reported in abstinent alcoholics and have not been reported to recover with prolonged abstinence.

There is a good deal of evidence indicating that ERP characteristics are genetically determined. Recently, Polich and Burns (23) reported that the P3 component of the ERP is more similar in identical twins than control subjects.

Thus, the reduced P3 voltage in high risk subjects perhaps provides a phenotypic marker for alcoholism. However, it remains to be determined whether those high risk individuals manifesting low P3 voltages are in fact those who go on to develop the disease of alcoholism. In order 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 not yet any compelling evidence demonstrating that those individuals manifesting low P3 voltages are in fact the ones who go on to become alcoholics. Longitudinal family studies are underway examining alcoholic and nonalcoholic families to determine which family members become alcoholic as they pass through the age of risk. It is hoped that with this approach the link between measures of risk and the development of alcoholism will be elucidated.

Thus, it seems that individuals at risk for alcoholism (sons of alcoholic fathers) can be distinguished from those not at risk for alcoholism on the basis of their P3 amplitudes without the ingestion of alcohol. While these electrophysiological measures may serve as phenotypic markers for alcoholism, it is not suggested that they are necessarily specific for alcoholism, nor is it suggested that all individuals manifesting these ‘‘markers’’ will necessarily go on to abuse alcohol. As these electrophysiological measures are genetically determined, these data imply that a predisposition or vulnerability to alcoholism is inherited. The role of environment and the gene-environment interaction are not to be minimized in determining whether an individual manifesting this predisposition goes on to abuse alcohol.

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