Event-Related Potential Evidence of Dysfunction in Automatic Processing in Abstinent Alcoholics

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The preattentive automatic processing of 63 alcoholics and 27 controls was evaluated with an auditory inattentive event-related oddball paradigm. We examined the mismatch negativity and the N2–P3 complex. Results showed significantly greater amplitude for N2, P3 and the N2–P3 complex for controls but no individual lead (Fz, Cz, Pz) differences by group. A group-by-lead interaction was found for N2 and for the N2–P3 complex. There were no significant latency differences between groups; however, a significant age-by-group interaction effect on latency was greatest at the Cz electrode. Results reflect a possible aberration of automatic processing in alcoholics because of a defect in the mnemonic template necessary to match with an infrequent deviant stimuli. We also found suggestive evidence of a relative weakness of frontal cortical organization in alcoholics. Future studies are suggested that would help clarify these differences in alcoholics.

Key Words: Auditory event-related potentials, alcoholics, automatic processing, frontal cortical deficit, mismatch negativity

Introduction

Electrophysiological measures of brain activity have been shown to be quite sensitive to the various effects of both acute (Fukui et al 1981; Porjesz and Begleiter 1973; Coger et al 1976) and chronic alcohol use (Bierly et al 1980; Begleiter and Porjesz 1977; Wagman et al 1978; Dustman et al 1979; Porjesz et at 1987a,b; Porjesz et al 1980a; Rogozea and Florea-Ciocoiu 1988). The evoked-potential literature on alcohol reveals significant differences in individuals with extensive drinking histories (for review, see Porjesz and Begleiter 1985). Of particular importance in understanding central nervous system functioning in abstinent alcoholics is determining the extent of deficits attributable to tasks requiring attention to stimuli or controlled tasks and those that reflect neural processes that are preattentive or automatic and not consciously perceived by the subject. These distinctions may tell us something of mechanisms that are beyond the alcoholic's awareness that nevertheless effect complex cognitive operations. Of particular importance in such a study is the work done with the mismatch negativity wave (MMN). The wave represents one component of the N2 wave. The early component of N2, the N2a, was found to be similar for both the attended and unattended experimental situations, suggesting that the wave reflected a preperceptual, "automatic" physiological representation of stimulus deviance elicited in a repetitive, homogeneous stimulus sequence (Naatanen et al 1978, 1980). The N2a or the mismatch

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was found to involve signal identification, whereas the later N2 component, called the N2h involves stimulus evaluation (Renault and Lesevre 1979). This later component, described as intentional or "controlled," is always followed by a positive deflection, the P3, forming a complex (Snyder and Hillyard 1976; Squires et al 1975). However, Naatanen showed that the N2a deflection was of equal amplitude to that of the N2b of the N2–P3 complex while it is elicited when the subject is not attending and cognitively diverted. Therefore stimulus significance or meaning was unnecessary for an N2a deflection. In addition, they showed that only the shortest interstimulus intervals (ISIs) elicited the MMN, whereas, ISIs of 4 sec or longer did not (Mantysalo and Naatanen 1987). They concluded that the MMN is produced by a comparison process occurring between the current deviant sensory input and some neuronal representation, a template, of the previous standard stimuli. The neuronal population eliciting the MMN must somehow have encoded the physical features of the standard stimulus (Naatanen 1986). The cerebral mechanism reflected by MMN seems to be one of passive detection of environmental change. The MMN might be regarded as the expression of an automatic preattentive comparative process. When the stimulus change is consciously observed, the arousal-related component may be reflected in the P3. This would be consistent with the work of Sams et al (1985). The auditory modality of this component has not been studied in alcoholics.

Paralleling these electrophysiological studies is evidence of frontal brain pathology demonstrated by various assessment approaches. Neuroanatomical data have shown the loss of specific acetylcholine receptors in the frontal cortex in alcoholics (Freund and Ballenger 1988). Positron tomography also showed abnormalities in this area by demonstrating lower glucose utilization in frontal cortical areas (Eckard et al 1988a,b). In addition, autopsy studies have also indicated prefrontal cortical involvement in chronic alcoholics (Courville 1955). However, some studies have shown more generalized atrophic changes (Harper and Kril 1985, 1990; Harper and Corbett 1990; Pfefferbaum et al 1988).

Another area within electrophysiology that has not received attention in alcoholism research is the N2–P3 complex (Sokolov 1966; Sams et al 1985). The N2–P3 complex is observed following the subject's reaction to a physically deviant stimulus interspersed in a sequence of repetitive stimuli. The N2–P3 is the result of a mismatch detector which signals any change in an ongoing background stimulus (Snyder and Hillyard 1976, p. 329). We report an unattended auditory paradigm, requiring no active participation of the subject, which was devised to collect N2–P3 complex electrophysiological responses that assessed signal identification and stimulus deviance.

Method

Subjects

The study subjects were recruited by the senior authors in an identical manner to previous studies of this kind. The experimental subjects were 63 alcoholic men between the ages of 17.7 and 50.79 years (mean = 34.65, SD = 7.05). They were recruited from the Addictive Disease Hospital of Kings County Hospital and were diagnosed by face-to-face interviews as Alcohol Dependent by DSM-III criteria. The subjects were solicited by mental health staff and offered a small monetary inducement for participation. Subjects were mostly black and Hispanic and had histories of comorbid conditions such as major depression, anxiety, and antisocial personality disorders. At the time of testing, no other psychiatric condition was active. The average time from last alcoholic intake was 31.4 days (SD = 20.77, range = 4–104 days). Seventy-six percent had a family history of alcoholism. Twenty-seven controls were hospital employees who responded to notices posted on bulletin boards or were recruited through local newspaper advertisements and were between the ages of 19.1 and 30.1 years (mean = 23.54, SD = 3.09). They were paid the same inducement as the experimental group. Subjects were interviewed and detailed questionnaires were administered to determine a history of medical and neurological disorders, use of medications, and drug and alcohol abuse. Exclusion criteria eliminated potential participants with medical problems, who were taking medications, or who used drugs.

Experimental Procedure

Subjects were seated in a sound-attenuated chamber and were asked to read a magazine of their choice. They were presented with two tones: (1) 240 high-pitched frequent tones (1000 Hz; 5 msec fall and rise times), and (2) 60 low-pitched infrequent tones (750 Hz). The frequent tone (high-pitched tone) represented 80% of the stimuli and the infrequent tone (low-pitched tone) made up the remainder. The tones were presented at a fixed interstimulus interval of 1.5 sec. The tones (50 msec duration) were presented binaurally through TDH Grass Instruments Co., Quincy, MA, headphones by means of a Grass click-tone control module (70 dB). Evoked potentials were averaged to these tones for 100 msec prestimulus and 1300 msec following the tone (sampling rate 200 points/sec; band width 0.1 - 100 Hz). On-line digital filtering was performed on the data between 0.1–30Hz. The event-related potentials (ERP) were amplified 20,000 times.

Electrodes

The Fz, Cz, and Pz electrodes were placed according to the international 10–20 system of electrode placement (Electro-Cap), with the nasion serving as reference and

the forehead as ground. Vertical and horizontal eye leads monitored eye movement contamination and trials with excessive eye movement (>75 μV) were automatically removed.

Data Analysis

Amplitude and latency values for this study were derived by visual inspection of each wave form for each subject at each electrode with collaboration of the senior investigator. Wave forms were plotted on paper and reviewed. Next the raw data was visually scanned by computer terminal and the cursor was placed at the point of maximal amplitude with the other two wave forms for that subject available for comparison. A software program then automatically displayed the amplitude and latency at the point of the cursor. Because of difficulties identifying a baseline from which to measure N2, and because there was no difference in the amplitude of P2 between groups, the peak of P2 was chosen as a landmark from which to measure N2 amplitude. Data analysis was performed on the amplitude and latency values of N2 measured from the peak of P2 to the trough of N2, and P3 measured baseline to peak to the infrequent tones at electrode sites Fz, Cz and Pz. The amplitude of the N2–P3 complex was measured from the trough of N2 to the peak of P3 in a manner similar to the measurement of N2. Peak amplitude and latency values were computed from subject averages. A multiple analysis of covariance (MANCOVA) with age as the covariate was computed for statistical differences between groups. Two-way analyses of variance (ANCOVA) with age as the covariate for group (alcoholics versus controls) and electrode (Fz, Cz, Pz) were computed for ERP component amplitude and latencies. A multiple regression analysis for age and electrode by group was performed to evaluate the effect of age on amplitude of N2 and P3. Also a correlation matrix was prepared to evaluate the relationship of amplitude of N2 and P3 and time of last drink.

Results

A comparison of the ages of the alcoholics and controls reveals a statistically significant difference (*t*-test for independent samples, $p < 0.001$). The experimental group was approximately 11 years older than controls. The adequacy of a covariate for age was statistically evaluated (Adams et al 1985). The results of a multiple regression analysis for age and amplitude showed a difference between groups for N2 at Pz (slope, $p = 0.045$; intercept, $p = 0.041$). For all other locations of N2 and P3, the use of the covariate was valid. Therefore, all further analyses were carried out with age as a covariate. The influence of age of the experimental group on amplitude of the experimental group can be demonstrated by Pearson correlation coefficients for the N2 and P3 infrequent tone at N2 and P3. Correlations were robust for N2: Fz, $r = 0.38$, $p = 0.002$; Cz, $r = 0.30$, $p = 0.02$; Pz, $r = 0.22$, $p = 0.075$; and for P3: Fz, $r = 0.32$, $p = 0.013$; Cz, $r = 0.18$, $p = 0.164$; Pz, $r = 0.14$, $p = 0.29$. For the control group, the effect of age on amplitude for N2 was: Fz, $r = 0.56$, $p = 0.002$; Cz, $r = 0.28$, $p = 0.16$; Pz, $r = -0.31$, $p = 0.13$; and for P3: Fz, $r = 0.077$, $p = 0.70$; Cz, $r = 0.107$, $p = 0.59$; Pz, $r = -0.20$, $p = 0.32$.

Grand means were computed for the two groups (see Figure 1).

Amplitude

Correlation coefficients and two-tailed significance tests demonstrated no relationship between the time of last drink for the alcoholic group and amplitude of N2 or P3. Also, there was no difference between the groups for the infrequent tone at Fz, Cz, or Pz for P1, N1, or P2 except for Fz ($p = 0.02$) and Cz ($p = 0.03$) at N1 at which alcoholics had greater negativity than controls (*t*-test for repeated measures). A comparison of the difference between frequent and infrequent tones at P1, N1, and P2 was not significant between groups.

A comparison of N2 waves generated by frequent and infrequent tones within groups yielded similar results. For both groups, the infrequent tone at N2 showed greater negative amplitude. The amplitude differences for the alcoholics and controls, respectively, were: Fz = 1.01, 0.48; Cz = 0.743, 0.37; Pz = 0.436, 0.695.

The following MANCOVA model was used to test amplitude effects: amplitude = b (group) + c (age) + d (age times group) with b = Fz, Cz, Pz. The mean amplitude of N2 was compared between groups for the infrequent tone. There was a significant difference between groups with controls showing greater negativity than alcoholics (MANCOVA—see model, Roy's Greatest Root, $F = 3.41$, df = 3, $p < 0.0212$). There was a group-by-lead interaction (MANCOVA, Roy's Greatest Root, $F = 4.518$, df = 2, $p<0.0137$). An ANCOVA with age as the covariate at individual leads showed controls with greater negativity than alcoholics at Fz ($t = 2.868$, $p < 0.0052$) and Cz ($t = 2.088$, $p < 0.039$) but no statistical differences at Pz (see Figure 2). However, the multiple regression analysis for age, slope, and intercept has shown that the covariate for age at Pz was not valid.

The mean amplitude of P3 for the infrequent tone was significantly larger for the controls compared to the alcoholic group (MANCOVA—see model, Roy's Greatest Root, $F = 8.1187$, df = 3, $p = 0.0001$). A MANCOVA showed no lead-by-group interaction for P3 (see Figure

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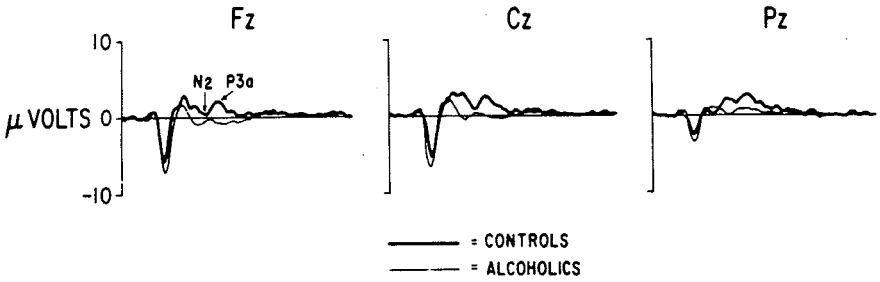

Figure 1. Inspection of the grand means reveals an N2 and a P3 wave for the infrequent tone condition in controls, but an insignificant or absent P3 wave for the alcoholics.

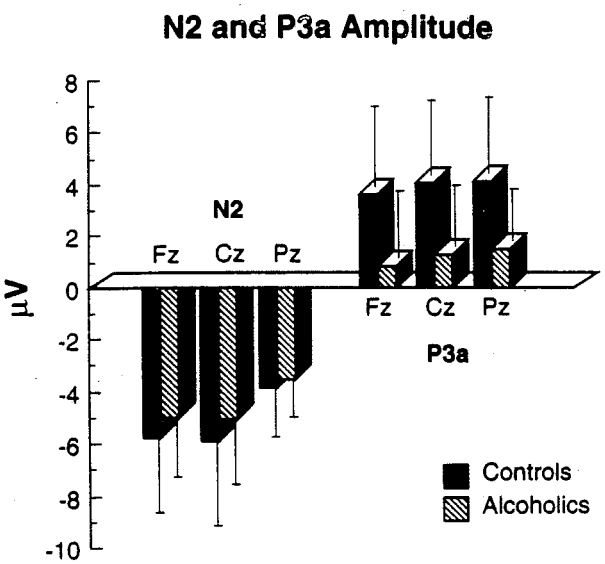

Figure 2. N2 amplitude: analysis shows a significant difference between groups (MANCOVA, Roy's Greatest Roots, $F = 3.868$, df = 3, $p < 0.0212$, group × age). P3 amplitude: analysis shows a significant difference between groups (MANCOVA, Roy's Greatest Root, $F = 8.1187$, df = 3, $p < 0.0001$).

2). ANCOVAs at individual leads showed no significant group differences.

The N2–P3 trough-to-peak amplitude difference was compared between alcoholics and controls for the infrequent occurring tone (see Table 1). A MANCOVA (see model) yielded an N2–P3 amplitude difference between groups with the controls demonstrating greater amplitude (Roy's Greatest Root), $F = 9.0277$, df = 6, $p = 0.0001$). A MANCOVA for the distribution of voltage among leads between alcoholics and controls showed a significant group-by-lead interaction (Roy's Greatest Root, $F = 6.2847$, df = 2, $p = 0.0029$). The ANCOVA at Fz showed significant group $t = -2.377$, df = 1, $p = 0.0197$) and a marginal group x age ($t = 1.935$, df = 1, $p = 0.0563$) effect. There was no significant difference at Cz or Pz (see Table 1).

Table 1. N2-P3 Amplitude (μv)

Electrode	Controls (SD)	Alcoholics (SD)
Fz	5.286 (3.742)	2.761 (1.726)
Cz	5.298 (2.838)	2.646 (1.645)
Pz	5.092 (2.585)	2.294 (1.453)

MANCOVA for the interaction of group and lead (Roy's Greatest Root, $F = 6.2847$, df = 2, $p = 0.0029$).

Latency

The mean latency between electrodes within groups was not different. The mean latency for N2 was not significantly different between groups for the infrequent tone using MANCOVA for group difference with age as the covariate. The mean latency for P3 was not significantly different between groups (MANCOVA for groups with age as covariate). A multivariate regression analysis for the effect of age-by-group interaction on N2 latency showed a statistically significant relationship at the Fz electrode ($F = 7.084$, $p = 0.0093$, $r^2 = .076$), at the Cz electrode ($F = 10.914$, $p = 0.0014$, $r^2 = 0.1126$) and at the Pz electrode ($F = 8.399$, $p = 0.0048$, $r^2 = 0.089$) (see Figure 3).

Discussion

Previous studies of the N2 and P3 ERP components in abstinent alcoholics during "controlled" or active attention paradigms have shown several electrophysiological anomalies by a number of researchers. In summary, these studies showed that alcoholics manifest two types of brain dysfunction: (1) a delay in N2 latency (Porjesz et al 1987a), which suggests that stimulus evaluation is defective, and (2) low P3 voltage, which suggests that the match/mismatch processes are themselves impaired (Pfefferbaum et al 1987; Patterson et al 1987; Porjesz et al 1987a; Porjesz and Begleiter 1981, 1982, 1983; Porjesz et al 1980a,b; Branchey et al 1988). This is the first study to report differences between alcoholics and controls using the passive oddball auditory paradigm. We found statistically significant decreased amplitude of N2, P3, and N2–P3 com-

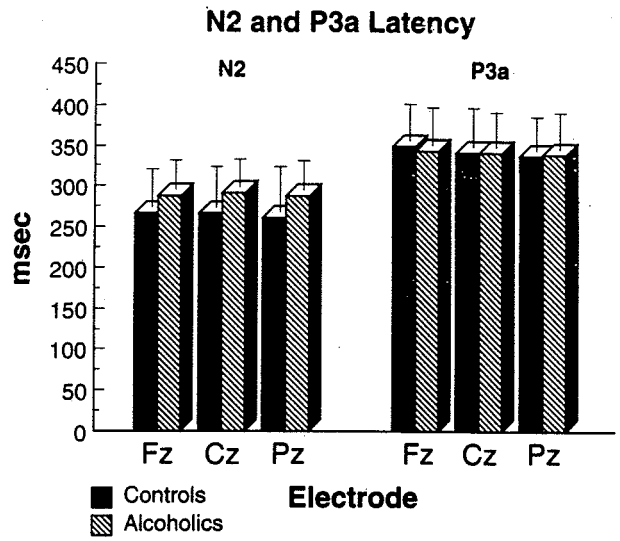

Figure 3. No significant differences between groups.

plex in alcoholics as compared to controls. However, further statistical analysis showed that the older age of the alcoholic subjects invalidated comparisons between the groups at Pz for N2 (see Results, p.8). Of further interest is the relationship of age and late-occurring potentials. The correlation coefficient for age and amplitude was most significant over the Fz electrode for both controls and alcoholics. However, the correlations at Pz for both N2 and P3 were in opposite directions between groups. With increasing age, the N2 amplitude showed greater negativity and the P3 amplitude showed less positivity for controls as expressed in the negative correlations at the Pz electrode. In contrast, for the alcoholics a positive correlations was found at Pz, but it was not significant for either N2 or P3. This suggests that an important difference in Central Nervous System (CNS) activity at the Pz site occurs with age in alcoholics. However, when age was covaried, differences between groups persisted only for N2, although not for P3 at the Fz site. The data may be suggesting that alcohol and age have an impact on topography at one site, but when age is covaried, there are widespread differences involving loss of both deviance detection and stimulus identification. Alcohol abuse had a greater effect on the detection of deviant stimuli at frontal sites. Our findings are consistent with those of other investigators who have reported decreased amplitude anomalies in alcoholics (Pfefferbaum et al 1987; Hill et al 1988; Porjesz et al 1980a; Porjesz and Begleiter 1981; Porjesz et al 1987a,b: Patterson et al 1987). What makes these results different, however, is the detection of differences from controls even when the subject was not attending to the stimulus, thus reflecting an aberration of automatic processing in alcoholics.

Our finding of lesser negativity of N2 in alcoholics suggests a deficient neuronal template. The template ...ay fail to form in the first place, rapidly decay, or be unusable. Because the MMN in normals decays in about 4 to 5 sec and our study presented stimuli with a short interstimulus interval of 1.5 sec, we postulate that his decay process is much swifter in the alcoholics and therefore the match/mismatch comparisons were not elicited. Because the preattentive process is dysfunctional, it follows that the P3, which is a function of an attentional switching process from these preattentive processes, would also be deficient in this group. This results in difficulties in evaluating the novel stimuli as different and by the corresponding poorly defined N2-P3 wave complex.

The P3 and its precursor N2 are thought to represent potentials elicited by the mismatch to the ongoing auditory stimulus train. This wave complex may be an index of a basic sensory mechanism that registers any change in background stimulus perhaps by means of mismatching a specific neural model established by repetition of the background (Squires et al 1975). The decreased amplitude of the N2-P3 complex presented in this study suggests defect in the mnemonic template such that the infrequent stimulus does not produce the mismatch to the extent found in controls.

Although decreased amplitude may provide clues about the electrophysiological deficits of alcoholics, examination of the distribution of the amplitude deficits may also be helpful. Both groups showed relatively greater P3 amplitude over the parietal electrode as has been described by others (Johnson 1989). However, based on the work of Knight and McCarthy, we expected to find greater frontal than parietal amplitude of our N2–P3 complex (Knight 1984; Knight et al 1981; McCarthy et al 1985; Wood and McCarthy 1985). Although the amplitude gradient of greater frontal than occipital potentials was in the expected direction for both groups, we found a statistically significant difference, greater amplitude for controls than alcoholics, only over the Fz electrode. This finding suggests another difference between controls and alcoholics, namely a relative weakness of frontal cortical organization of the N2–P3 as compared to controls. This difference could be interpreted as a deficit resulting from an undifferentiated neural generator without an established specific locus or the demonstration of a specific frontal cortical deficit. Secondary generators for P3 arising from frontal cortex, which are sensitive to aging and alcoholism, have been demonstrated by Sidman et al (1991). This finding is consistent with evidence of frontal deficits in alcoholics demonstrated by several techniques (Freund and Ballenger 1988; Eckardt et al 1988a,b: Courvill 1955; Volkow et al 1992; Harper and Corbett 1990; Harper and Kril, 1985, 1990; Pfefferbaum et al 1988). Behavior related to frontal deficits has been documented by numerous neuropsychological as-

sessments, which consistently show deficits in abstraction as well as other cognitive functions (Fitzhugh et al 1965; Jones and Parson 1971; Long and McLachlan 1974; Smith et al 1973; Acker et al 1984; Parsons and Leber 1981, 1982).

We found no relationship between the time of last drink and decrements in late ERP components. Although acute alcoholization in normal healthy subjects prolongs latency and diminishes amplitude at various levels of the CNS, our findings in "abstinent" alcoholics are consistent with normalization of acute alcohol effects on latency but continued decrements in amplitude.

Although the latency of N2 was longer for alcoholics than controls, this difference did not reach significance when age was used as the covariate, nor were the P3 latencies different between groups. An analysis for the interaction of age and group for N2 latency was significant. The greatest contribution of age to the variance of latency was found at the Cz electrode, accounting for 11% as compared to 7% and 8% for the Fz and Pz electrodes, respectively. Our results suggest that age has an important influence on latency and can confound the interpretation of the effect of chronic alcoholism on the latency of ERPs. These results are consistent with studies that show age-related latency changes in both the auditory and visual modalities (Sidman et al 1990, 1991).

This study has several limitations that compromise the strength of the findings. The determination of wave forms for the leads of interest Fz, Cz, and Pz were accomplished through careful inspection of each subject's wave form in collaboration with the senior investigator. However, the investigators were not blind to group assignment and some unforseen bias may have contributed to the findings. Another concern is the large difference in age between groups, and therefore the results of this article should be considered cautiously. Although statistical correction for age was accomplished, it may have obscured important differences between groups. Further statistical analysis showed that this model-based correction was inadequate for comparison of the N2 wave at the Pz location. Also differences in ethnicity and socioeconomic status between groups, which can be correlated to IQ and attentional factors, may have influenced results in ways that were not examined in this study.

In summary, our findings of decreased amplitude of the N2–P3 complex and decreased amplitude at the frontal lead suggest a deficit of preperceptual, automatic, and subsequent mismatch processes. This hypothesis has heuristic value in that future studies may systematically investigate preattentive processes in alcoholics by varying the ratio of frequent-to-rare stimuli, the degree of physical deviance of the stimuli, and the time interval between the frequent and rare stimuli. These studies would be useful in clarifying the nature, extent, integrity, and generator of this functionally defined entity and how it differs in alcoholics.

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