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Auditory P300 in Young Alcoholics: Regional Response Characteristics

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An auditory oddball paradigm was used to record the P300 component of the event-related potential (ERP) in a group of medication-free, chronic male alcoholics (n = 51, mean = 32.2) and a control group (n = 25, mean = 27.2). Each subject received a binaurally presented series of high (1600-Hz)- and low (600-Hz)-frequency tones. The designation of the rare tone (0.125 probability) was alternated across subjects. When the subject detected the rare tone, he made a button press as quickly as possible to record his reaction time. Scalp recordings using the entire 10/20 System, as well as interpolated placements, were made from 31 electrodes. For purposes of statistical analyses, five regional electrode groups were created: F (frontal), C (central), P (parietal), O (occipital), and T (temporal). The results of MANOVA indicated that control P300 amplitudes were significantly greater than those of the alcoholics in all five regions, whereas there were no P300 latency differences between groups in any region. Regional response differences between the groups were also compared with measures of surface energy (SE) (Wang et al., 1994). SE is a recently developed, reference-free global field measure that uses the entire scalp potential field and treats potentials at different positions differently. SE was significantly reduced in the alcoholics compared with the controls in both the C (p < 0.0003) and P (p < 0.0006) regions, although there were no differences in its distribution. Within the alcoholics, we identified a low-density (LD; n = 16) and high-density (HD; n = 22) subgroup based on the number of their alcoholic relatives (LD, no alcoholic relatives; HD mean = 4.4 alcoholic relatives/individual). Statistical analyses revealed that, in the O region, LD individuals had significantly larger P300 amplitudes than did HD individuals. Moreover, although there were no differences between LD and control P300 amplitudes in any region, HD subjects had significantly reduced P300 amplitudes compared with controls in every region. These findings suggest that genetic factors may contribute to the deficits observed. Moreover, these deficits may precede the onset of alcoholism and may function as critical phenotypic markers for its development.

Key Words: P300, Auditory Oddball, Alcoholic, Surface Energy.

INVESTIGATIONS OF event-related potentials (ERP) in chronic, abstinent alcoholics have often documented reductions in component amplitudes and less frequently, increases in component latencies.[1] One of the most widely studied ERP components is P300. In healthy individuals, P300 latency ranges from 300 to 500 msec and is maximal over parietal regions. P300 characteristics seem to reflect factors related to the subjective significance of the stimulus, such as task relevance,[2] unpredictability,[3] infrequency,[4] and motivational factors,[5] and can even be elicited in the absence of an expected stimulus.[6]

In chronic alcoholics, the most frequently documented changes in the P300 response are reduced amplitude in the absence of latency changes.[7–11] These observations result largely, but not exclusively, from experiments utilizing various information processing paradigms, including the oddball paradigm. The deficit has most consistently been observed in visual paradigms;[7,8,11–14] less consistent results have been obtained for auditory paradigms, with reports of both reduced[11,14–17] and normal[18,19] P300 amplitudes, although the latter two studies[18,19] reported increased latencies. Analyses of single trial-evoked responses[9,14,20–22] revealed that the reduction in average P300 amplitude reflected decreases in single trial amplitudes, rather than increased variability in latency. Based on recent evidence that the neural generators of auditory and visual P300 may be different,[23] it has been suggested[14] that the modality-related differences in the results may indicate that the neural generators are differentially sensitive to the effects of ethanol.

At one time it had been suggested that the reduced P300 amplitude manifested by chronic alcoholics reflected high lifetime ethanol consumption. However, the recent results of a path analysis[14] suggested that family history, rather than lifetime ethanol consumption, was more important in determining P300 reduction. Interestingly, the family history negative (FH−) alcoholics in this study generated P300 amplitudes at the Pz electrode as large as those recorded in the control population. Thus, it was hypothesized that studies of chronic alcoholics that could not demonstrate reduced P300 amplitudes may have used individuals who were either FH− for alcoholism or low density (LD) of alcoholic family members. Additional evidence for the contribution of family history to reduced P300 amplitude comes from a recent meta-analysis of P300 from males at risk for alcoholism.[24] The analysis, utilizing data from more than 20 studies, evaluated factors such as the diagnostic criteria used to assess alcoholism in the subject's biological relatives, subject age, stimulus modality, and task difficulty. The study concluded that, based on the available evidence, individuals with a positive family history (FH+) of alcoholism generally demonstrated smaller P300 amplitudes than individuals without a family history of alcoholism.

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The fact that family history can influence the reduction in P300 amplitude suggests that genetic factors may contribute to this deficit. Initial evidence that reduced P300 amplitude may be a phenotypic biological marker for the development of alcoholism came from a study[25] wherein reduced P300 amplitudes were recorded in the unaffected male children (ages 7–13) of chronic alcoholics. Subsequent studies in the same lab in young[26] (ages 7–13) and older[27] (ages 18–23) sons of alcoholic fathers without ethanol administration, replicated the earlier results, as have numerous studies in other laboratories.[28–32] P300 latency has been defined as a relative index of stimulus processing time[33] and a measure of the speed with which attentional resources are both allocated and maintained,[34] and may be influenced by variables such as subject age and task difficulty.[14,34]

The electrophysiological responses documented in all of the aforementioned studies reflect the recordings of scalp potentials (SPs) at a finite number of electrode sites. These recordings, which likely reflect the average activity of multiple neural sources recorded at a distance, are neither reference-free, nor independent of the volume conductor effects of the brain, skull, and scalp. These limitations mean that: (a) SPs recorded from different subjects, experimental conditions, or time points cannot be compared because they are not derived from a common base;[35] (b) ERP components will be altered if the placement of the reference is changed or if it is not a "quiet" reference;[36] and (c) there may be spatial smearing of the potential record as a consequence of volume conductor effects. To eliminate these problems, measures of neural activity have been developed that are both reference-free and independent of any physical conductive head models. Scalp current density (SCD) presents both scalp sources and sinks of current, but mainly reflects cortical generators; a scalp region having a positive current density corresponds to a source region where a local radial current is flowing through the skull into the scalp. Surface energy (SE)[35] is a newly developed global field measure that uses the entire SP field and treats potentials at different positions differently. Because SPs are only recorded at finite electrode sites, they may not capture all the important properties of the SP field. However, with the use of interpolating techniques, we can obtain a good approximation of the true, entire SP and SCD fields. Herein, the spherical spline method[37,38] is used to obtain an SP field by finding a smoothing spline on the sphere with the smallest bending energy and passing through the recorded potential at electrode sites on the scalp. Due to the properties of the spline, the interpolated SP or SCD field (by using recorded potentials at the electrode sites on the scalp) is a good approximation of the true SP or SCD field if the number of sites is large enough. Therefore, it is reasonable to assume that a global measure based on the entire interpolated SP or SCD field should represent the true SP or SCD field better than that based on only finite electrode sites. SE is based on the spherical spline and the entire interpolated SCD (the surface Laplacian of SP) field. The SE gives a global field measure, and an SE wave in a time interval shows continuous time elements and can, for example, be used in topographic component recognition. Thus, SE is analogous to the bending energy of the SP field, uses the entire SP field, and treats potentials at different positions differently (see the Appendix for the interpolation algorithm used for determination of SE).

In this study an auditory oddball paradigm was used to elicit the P300 component of the ERP in a population of abstinent, chronic alcoholics and a control group. Regional response differences between groups were assessed by MANOVA and measures of SE. Moreover, we assessed the effect of family history on regional P300 morphology.

METHODS

Subjects

The subjects in this study were 76 right-handed males ranging from 20 to 50 years of age. Control (n = 25, mean = 27.7) individuals were recruited either through newspaper ads or via notices posted in the Health Science Center. The initial screening procedure required each prospective subject to fill out a questionnaire detailing alcohol and drug use, and the medical and psychiatric histories for both himself and his relatives. Inclusion in this group initially depended on both the responses to the questionnaire and the requirement that none of the control candidate's first- or second-degree relatives be diagnosed as alcoholic. In contrast, the alcoholic (n = 51, mean = 32.2) group consisted of individuals undergoing 30 days of treatment in the Short-Term Alcohol Treatment Unit, Addictive Disease Hospital, Kings County Hospital Center. The alcoholics were significantly older than the controls ($p < 0.0001$) and had an early onset of drinking (mean = 14.5 years). Individuals in this program were put on a regimen that included vitamin and nutritional therapy, and were monitored closely for any signs of drug and/or alcohol abuse. Typically, participants in the study were tested on their 28th day in the program, or as close as possible to their release. Each individual was required to give his informed consent and was paid for his services. For this group, exclusionary criteria for the study included a history of intravenous drug use; treatment medication, such as antabuse, psychoactive drugs, or drugs with CNS effects; seizures unrelated to withdrawal, retardation, hearing, or visual impairments; and liver damage (e.g., cirrhosis). Exclusionary criteria for both the alcoholic and control groups included major medical problems, a current requirement for medication that affected the CNS, or a history of psychiatric problems and/or drug abuse (a degree of drug abuse was permitted if secondary to the alcoholism). Upon meeting the aforementioned criteria, each subject was invited to the laboratory, wherein he underwent a detailed psychiatric interview focusing on questions of drug and alcohol use (quantity/frequency data), and the medical and psychiatric histories for both himself and his first- and second-degree relatives. Some of the subjects (both alcoholics and controls) were members of entire families participating in a national project regarding the genetics of alcoholism (Collaborative Study on the Genetics of Alcoholism). Each participating family member was interviewed with the Semi-Structured Assessment for the Genetics of Alcoholism, which uses both DSM-III-R and Feighner criteria for the determination of alcoholism. Interviews with the additional family members helped to document our family history information.

Experimental Design

The subject was seated comfortably in a dimly lighted, temperature-regulated, sound-attenuated chamber (Industrial Acoustics Corp.). He was told to keep his eyes focused on a fixation target centrally displayed on a computer monitor (Concurrent Computer Corp., Oceanport, NJ). Each

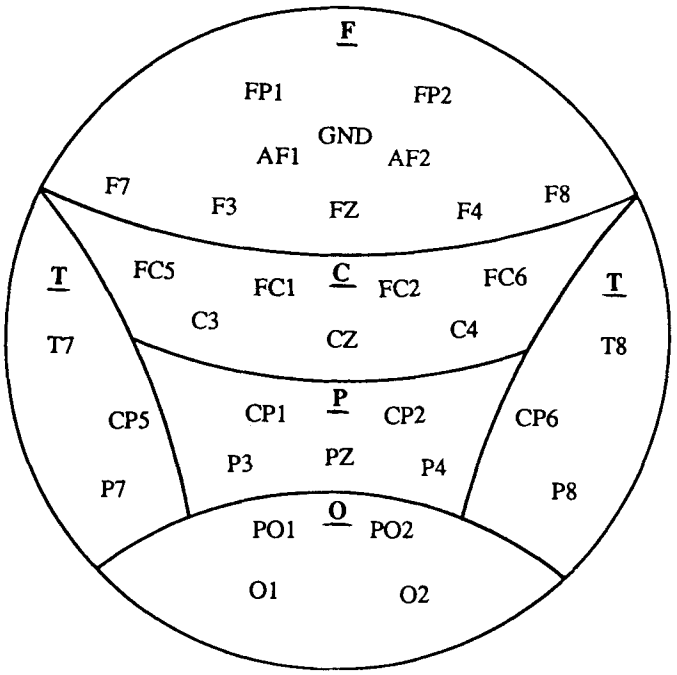

Fig. 1. The recording electrode (n = 31) montage and the regional groupings (F = frontal, C = central, P = parietal, O = occipital, and T = temporal) used in the statistical analyses.

subject wore a fitted electrode cap (Electro-Cap Intl., Inc., Eaton, OH) containing 31 electrodes. Figure 1 presents the recording electrode montage and the regional electrode groupings used in the statistical analyses. The nasion served as reference and the forehead as ground. Both vertical and horizontal eye movements were monitored. EEG activity was amplified 20 K (Sensorium EPA-2 Electrophysiology Amplifier; bandpass 0.2–100 Hz). Baseline activity was continuously sampled at a rate of 256 Hz, beginning 187 msec before stimulus onset and continuing for 1.5 sec. The ERPs to each stimulus presentation were monitored continuously. Subjects were warned not to blink their eyes and to sit still. Both digital filtering (32-Hz low-pass) of the raw data and artifact rejection (EMG, EOG, and saturation artifact > 73.3 μV) were performed on-line.

The two binaurally presented stimuli consisted of a 600 Hz (low) tone and a 1600 Hz (high) tone produced by a tone generator designed and constructed on site (Scientific and Medical Instrumentation Div., Health Science Center, Brooklyn, NY). Each stimulus had a 60-msec duration (10 msec rise and fall time, 40 msec plateau) and an intensity level of 60 dB SPL. A computer (Concurrent Computer Corp.) initiated the stimuli with a uniform interstimulus interval of 1.5 sec. The rare tone and frequent tone had 0.125 and 0.875 probabilities of occurrence, respectively. The designation of the low- or high-frequency tone as the rare stimulus was alternated across subjects. Each subject was read the following instructions:

"You are going to hear two different tones. One of them is a high tone, the other is a low tone. The tones will be presented, one at a time, to both ears. When you hear the high (low) tone, please respond to it as quickly as possible by pressing the button under your right hand. Be careful to respond only to the high (low) tone. Do not respond to the low (high) tone."

The auditory stimuli were presented binaurally through headphones (Etymotic Research, Elk Grove Village, IL, model ER-3A Tubephone Insert Earphones, 50 ohms impedance) in which only the earpiece and a short length of the Tubephone were fitted under the electrode cap; the individual left and right transducer cases were situated on either side of the neck. When the subject detected the rare tone, he responded by depressing a button on a modified computer mouse as quickly as possible.

Table 1. Subject Characteristics of the Controls (C), All Alcoholics (A), LD Alcoholics, and HD Alcoholics

	C (n = 25)		A (n = 51)		LD (n = 16)		HD (n = 22)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (yr)	27.7	3.8	32.1	5.7	32.6	5.6	33.6	6.2
Education (yr)	16.4	2.8	11.4	2.0	11.7	2.4	11.5	2.2
Age at onset of drinking (yr)	NA	NA	14.5	3.1	14.6	3.0	14.4	3.2
Drinking days/month	3.4	3.0	22.9	9.9	24.3	9.2	21.2	11.2
Drinks/occasion	2.1	2.2	12.0	6.3	12.8	6.7	10.0	5.6

NA, not applicable.

This action terminated a clock whose onset was simultaneous with stimulus onset and recorded the reaction time (RT). The subject received a maximum of 400 trials, but the experiment could be terminated after as few as 70 artifact-free trials (a minimum of 20 target and 50 nontarget trials) were acquired. Response speed was emphasized, but not at the cost of accuracy. Trials with RTs >1000 msec were rejected. The ERPs and RTs from accepted trials were automatically placed in one of two categories for subsequent averaging and statistical analysis.

Data Analysis

For each subject, the average ERPs derived from the target stimuli in the rare condition were analyzed via an automatic peak detection program. The P300 component was selected as the largest amplitude peak within a time window from 250 to 500 msec. Thus, each subject's data consisted of peak voltages (μV) and latencies (msec) at each of 31 electrodes.

To characterize the responses occurring at the 31 electrodes, five regional groupings were created: *frontal*—FP1, FP2, AF1, AF2, F3, F4, F7, F8, Fz; *central*—FC5, FC6, FC1, FC2, C3, C4, Cz; *parietal*—CP1, CP2, P3, P4, Pz; *occipital*—PO1, PO2, O1, O2; and *temporal*—T7, T8, CP5, CP6, P7, P8 (see Fig. 1). MANOVAs (SAS ver. 6)[39] were used to assess group differences in P300 amplitude and latency in each of the aforementioned regions. ANCOVAs were used to determine if P300 amplitude covaried with age. Regional differences between both groups were also assessed via measures of SE.[35] Independent group t tests were used to evaluate differences in both RTs to the target stimulus and in error rates, including missed target stimuli and incorrect responses (i.e., presses to nontarget stimuli).

The effect of family history on P300 regional response amplitude was examined by comparing the responses of the low-density (LD) and high-density (HD) groups. An individual in the LD group (n = 16) could not have had any alcoholic relatives. In contrast, a member of the HD group (n = 22) had to have three or more alcoholic relatives (mean = 4.4 relatives/individual). There were neither any differences in the ages of the two groups (LD, mean = 32.6; HD, mean = 33.6) nor in their ages at the onset of drinking (LD, mean = 14.6; HD, mean = 14.4). Both MANOVA and measures of SE were applied to the LD and HD alcoholics. Table 1 presents subject characteristics for the controls, all alcoholics, LD alcoholics, and HD alcoholics.

RESULTS

Controls Versus Alcoholics

The regional analyses of P300 characteristics in the target condition demonstrated that P300 amplitudes in the control group were significantly greater than those in the alcoholic group in each of the five regions: frontal ($p < 0.006$), central ($p < 0.011$), parietal ($p < 0.0008$), occipital ($p < 0.0036$), and temporal ($p < 0.0081$). In contrast, there were no group differences in P300 latency in any region.

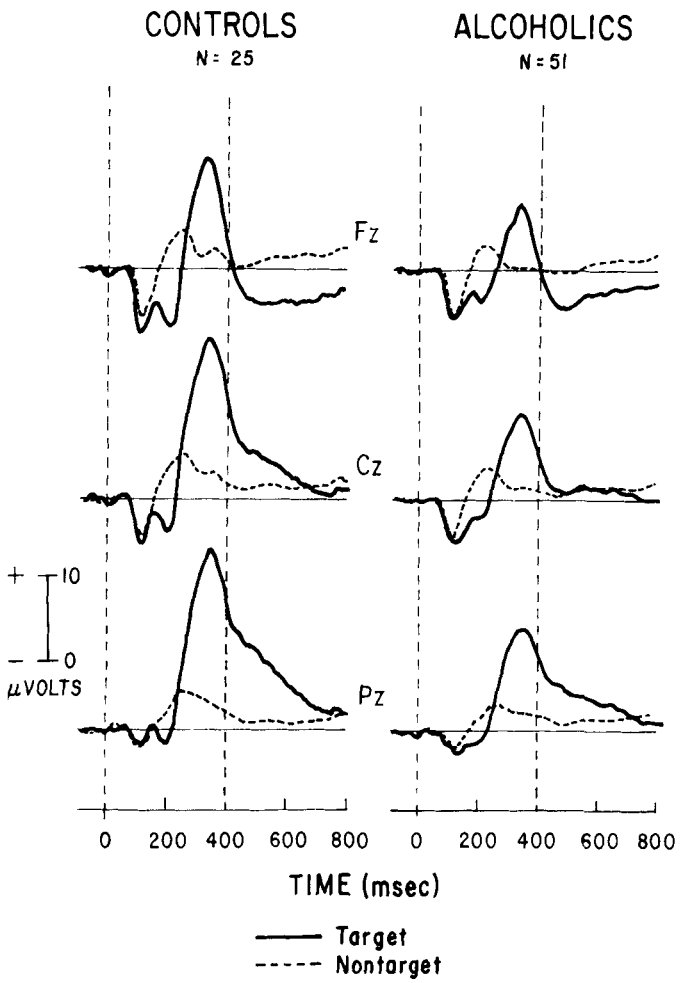

Fig. 2. Mean ERP waveforms for the target condition (solid line) and nontarget condition (dashed line) for control (left) and alcoholic (right) individuals at electrodes Fz, Cz, and Pz. Positive (+) is up.

Figure 2 presents the mean ERP waveforms for the control and alcoholic groups at electrodes Fz, Cz, and Pz. Moreover, the results of ANCOVA indicated that response amplitudes did not covary with age. Furthermore, whereas there were no group differences in RT, a comparison of error rates revealed that the alcoholics missed significantly more target stimuli than did the controls ($p < 0.013$), although there were no group differences in the number of incorrect responses (i.e., presses to nontarget stimuli).

SE

Figure 3 presents SE as a function of time (msec) for both control ($n = 25$) (left) and alcoholic ($n = 51$) (right) individuals under the target condition. For each group, the earlier of the two peaks, which occurs between 325–375 msec, corresponds to the period of peak P300 amplitude. It can be observed that the magnitude of SE in the control group is nearly 2.5 times that in the alcoholic group. In each panel, the later peak, occurring between 450–500 msec, likely reflects slow wave activity. The results of MANOVA indicated that the amount of SE in the controls as compared with the alcoholics was significantly greater in both the central ($p < 0.0003$) and parietal regions ($p < 0.0006$). Significantly greater magnitudes of SE were observed at central electrodes C3 ($p < 0.008$), FC1 ($p < 0.017$), and FC2 ($p < 0.038$) and parietal electrode CP1 ($p < 0.00001$).

Table 2. Mean P300 Amplitudes (μV) for the Control (C), Alcoholic (A), LD Alcoholic, and HD Alcoholic Groups at Representative Electrodes

	C (n = 25)		A (n = 51)		LD (n = 16)		HD (n = 22)	
Electrode	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Fz	15.4	6.2	10.1	5.7	10.4	6.0	9.2	4.4
Cz	20.2	6.4	12.9	6.6	13.4	6.9	12.2	5.8
Pz	22.5	5.6	14.8	7.0	15.6	6.3	14.0	6.6
PO1*	19.6	5.4	13.2	6.4	14.0	5.9	12.2	5.7
PO2*	19.4	6.2	13.1	6.6	14.6	5.6	11.7	6.2
O1*	14.7	5.4	10.4	6.0	11.6	4.6	9.1	5.1
O2*	14.6	5.8	10.0	5.5	11.4	4.2	8.6	5.0

* These electrodes comprise the occipital region in which a significant amplitude difference was found between LD and HD alcoholics.

Table 3. Comparisons of Regional P300 Amplitudes for Controls (C; n = 25), All Alcoholics (A; n = 51), LD Alcoholics (n = 16), and HD Alcoholics (n = 22)

Region	C vs. A	LD vs. HD	C vs. LD	C vs. HD	C vs. LD vs. HD
Frontal	0.006	NS	NS	0.007	NS
Central	0.011	NS	NS	0.037	NS
Parietal	0.0008	NS	NS	0.005	0.031
Occipital	0.004	0.012	NS	0.009	0.024
Temporal	0.008	NS	NS	0.015	NS

LD Versus HD Alcoholics

Regional analyses of P300 response characteristics revealed that the HD alcoholics, compared with the LD alcoholics, had significantly decreased P300 amplitudes ($p < 0.0125$) in the occipital region (electrodes PO1, PO2, O1, and O2). There were no group differences in P300 latency in any region nor in the RTs of the two groups. Although there were no statistically significant differences in the error rates of the two groups, the HD group, in contrast with the LD group, missed significantly more target stimuli ($p < 0.027$) than the control group. In contrast to the findings in the controls and alcoholics, measures of SE in the LD and HD alcoholics indicated no differences between the groups.

To determine whether the differences in P300 amplitudes between controls and alcoholics were related to differences in the density of alcoholic relatives, comparisons were made between controls, LD alcoholics, and HD alcoholics. Table 2 presents mean P300 amplitudes for controls, all alcoholics, LD alcoholics, and HD alcoholics at representative electrodes. Table 3 summarizes the results of these group comparisons, as well as those between the controls and the entire group of alcoholics. Because P300 amplitude, rather than P300 latency, effectively discriminated among the groups, only the results of the former comparisons are presented. What is most interesting is the fact that group differences, manifested as a reduction in P300 amplitude, seem to reflect family density. Although

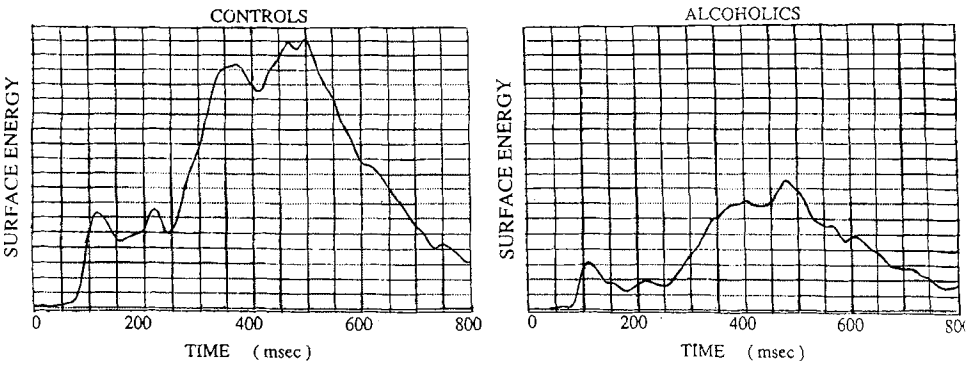

Fig. 3. SE, analogous to the bending energy of the SP field, measured during the target condition, is presented as a function of time (msec) for both controls (left) and alcoholics (right). Peak SE amplitude measured over the interval of peak P300 amplitude (325–375 msec) in the control group is ~2.5 times that in the alcoholic group. The peak occurring between 450 and 500 msec likely reflects slow wave activity. Each time division is 50 msec.

comparisons between LD alcoholics and controls evidenced no regional differences in P300 amplitude, comparisons between HD alcoholics and controls documented significant amplitude reductions in every region.

DISCUSSION

This study demonstrates that there are widespread, significant differences in P300 morphology between abstinent, chronic alcoholics, and control individuals. The alcoholic group had significantly decreased P300 amplitudes in each of the five scalp regions examined, without significant differences in P300 latency. Measures of SE also documented differences between controls and alcoholics; over the interval from 325 to 375 msec when P300 amplitude was maximal, the controls had ~2.5 times more SE than the alcoholics (see Fig. 3). Moreover, significant local differences were observed in both the central and parietal regions. Lastly, although there were no group differences in RT, the alcoholics missed significantly more target stimuli than did controls. In comparing P300 responses between the LD and HD alcoholic subgroups, we observed that the HD group had significantly reduced P300 amplitudes in the occipital region (electrodes PO1, PO2, O1, and O2). When the responses of the LD and HD alcoholics were compared with those of the control group, the LD group did not differ significantly from the controls in any region, but in contrast, the HD group manifested reduced P300 amplitudes in each region.

Reduced P300 amplitude is the most common observation in abstinent, chronic alcoholics.[1,7–15,17,22,40] Typically, most previous studies in alcoholics have utilized a fairly small number of recording electrodes and found amplitude reductions in both the central and parietal regions, where P300 is most prominent.[41] With the 31 electrode recording montage used herein, we were able to demonstrate a more extensive deficit than has previously been reported. However, it is interesting to note that the SE deficits seen in the alcoholics were localized only to the parietal and central regions.

In general, there have been two interpretations of the P300 deficit observed in alcoholics. The earlier one suggested that the deficit may reflect the sensitivity of the neural generator(s) of P300 to the neurotoxic effects of alcohol. Thus, it might be assumed that with abstinence there might be an improvement in P300 amplitude. However, in two studies,[22] one in which hospitalized, abstinent alcoholics were examined at both 3–4 weeks and at 4 months after initial testing, and another in which nonhospitalized sober alcoholics were examined following 3–10 years of abstinence, P300 amplitude still remained low. In contrast, brain stem auditory-evoked responses, which were also recorded, presented with increased latencies and decreased conduction velocities that returned to near normal values with prolonged abstinence. Thus, it may appear that the neurons comprising the auditory pathway, and the neural generator(s) of P300, are differentially sensitive to the neurotoxic effects of ethanol. However, a more recent, alternative interpretation of the deficit in P300 derives from the substantial evidence[1,25,26,28,30–32,42,43] that reduced P300 amplitude is a highly heritable trait that antecedes the development of alcoholism and may be considered as a critical phenotypic marker.[14,44,45] Given these findings, the P300 response characteristics in the LD and HD alcoholics are quite interesting. Although both groups had similar drinking histories, with nearly identical ages for the onset of drinking (LD, mean = 14.6; HD, mean = 14.4), the LD alcoholics had no alcoholic relatives; the HD alcoholics had mean = 4.4 alcoholic relatives/individual. When the regional responses of each group were compared with those of the control group, the HD group manifested significant amplitude reductions in each region, whereas the LD group had none (see Table 3). This suggests that genetic factors may underlie the group differences in P300 amplitude. Evidence for the possibility of a genetic contribution to both EEG and ERP morphology comes from both investigations of alcoholics and their relatives[46,47] and from twin studies.[48,49] For example, one study[46] observed that both baseline EEG activity and the EEG response to an ethanol challenge were more similar in monozygotic (MZ) than dizygotic (DZ) twins, whereas another documented that more similar EEG variants were observed both in alcoholics and their nonalcoholic first-degree relatives than in alcoholics and matched controls.[47] In two studies using an auditory oddball paradigm,[48,49] the former[48] reported that both P300 amplitudes and latencies were sig-

nificantly correlated in MZ twins as compared with control pairs, whereas the latter[49] demonstrated significant heritability of P300 amplitude, latency, and wave shape, with responses of MZ twin pairs more similar than those of DZ twin pairs. A recent study[14] ruled out both lifetime alcohol consumption and the intensity of drinking as major codeterminants of P300 amplitude reduction. It was observed that when alcoholics were classified either as FH+ or FH−, FH− individuals had P300 amplitudes at the Pz electrode as large as those of control individuals, a finding similar to that of the present study. Moreover, those who were FH+, generated P300 components as often as FH− individuals, but the individual components were reduced in amplitude. The contribution of family history to the reduction in P300 amplitude is strongly supported by our results.

In conclusion, the results of our study indicate that, abstinent, chronic alcoholics differ electrophysiologically from control individuals. These differences are manifested as widespread reductions in P300 amplitude and localized reductions in SE. When family history (i.e., density of alcoholic relatives) was used to characterize two alcoholic subgroups, only those alcoholics with a HD of alcoholic relatives had widespread decreases in P300 amplitudes when compared with the control group. Our findings suggest that these deficits may precede the onset of alcoholism and may function as critical phenotypic markers for its development.

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APPENDIX

The interpolation algorithm used for the determination of SE is as follows:

$$SE = \int_0^{2\pi} \int_0^{\frac{\pi}{2}} (\Delta SSP)^2 \sin(\varphi)\, d\varphi d\Theta,$$

where Δ is the restriction of the Laplacian in three-dimensional space to the surface of the sphere, and SSP is the spherical spline potential interpolated from the recorded potential at electrode sites by use of the spherical spline method.[37,38]

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