Neuroelectric Correlates of Response Production and Inhibition in Individuals at Risk to Develop Alcoholism

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P300 recordings were made from males at high risk (HR) for alcoholism and low-risk (LR) controls, participating in a visual go/no go reaction time paradigm. The go (button press) and no go (inhibit response) stimuli were large and small forms of the same letters. The LR group had significantly larger go than no go P300 amplitudes in the central, parietal, and temporal regions; the HR group manifested no response differences in any region. In the LR group compared to the HR group, both go and no go response amplitudes were larger over the entire head; no group differences in latencies were observed in any region. Surface energy magnitudes paralleled P300 amplitudes and were also larger in the LR group during both go and no go trials. Our findings indicate that HR individuals manifest widespread P300 amplitude deficits while performing a simple information-processing paradigm. These deficits, which may reflect genetic influences, preceded the onset of alcoholism and may function as a phenotypic marker for its development. © *1997 Society of Biological Psychiatry*

Key Words: P300, alcoholism, go/no go, surface energy

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Introduction

Investigations into the electrophysiological differences between individuals at high risk (HR) for the development of alcoholism and a matched, low-risk (LR) control group have often proceeded by comparing the P300 component of the event-related potential (ERP). Begleiter et al (1984) demonstrated that P300 amplitude is reduced in the unaffected male children (ages 7–13) of chronic alcoholics without the administration of ethanol. Subsequent studies in the same lab in young (Begleiter et al 1987) (ages 7–13) and older (Porjesz and Begleiter 1990; Ramachandran et al 1996) (ages 18–23) sons of alcoholic fathers, without ethanol administration, replicated the earlier results, as have numerous studies in other laboratories (O'Connor et al 1986, 1987; Hill et al 1988; Hill and Steinhauer 1993; Whipple et al 1988, 1991; Noble et al 1990; Berman et al 1993). In contrast, a limited number of studies have had either negative or equivocal results (Polich and Bloom 1987, 1988; Polich et al 1988; Hill et al 1990). Recently, Polich et al (1994) performed a meta-analysis of P300 in individuals at high risk for alcoholism. The analysis examined the results of 22 studies and evaluated factors

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such as the diagnostic criteria used to assess alcoholism in the subject's biological relatives, subject age, task difficulty, and stimulus modality. The authors concluded that based upon the available evidence, individuals with a positive family history of alcoholism generally demonstrated reliably smaller P300 amplitudes than individuals without a family history of alcoholism. The results of a path analysis (Pfefferbaum et al 1991), which compared P300 responses in family history positive (FH+) and family history negative (FH−) alcoholics, suggested that family history, rather than lifetime ethanol consumption, was more important in determining the reduction in P300 amplitude. Lastly, Cohen et al (1995) examined the P300 responses of two groups of abstinent, chronic alcoholics in an auditory oddball paradigm. Only the high-density alcoholics (4.4 alcoholic relatives/individual), compared to the control group, had significantly decreased amplitudes. In contrast, the low-density alcoholics (no alcoholic relatives/individual), compared to the control group, manifested no statistically significant amplitude differences. Together, these studies suggest that the influence of genetic factors may contribute to the deficit in P300. Moreover, it has been hypothesized that the deficit is a highly heritable trait that antecedes the development of alcoholism, and may be considered as a biologic phenotypic marker for the development of alcoholism (Begleiter and Porjesz 1988; Pfefferbaum et al 1991).

Most studies that have compared P300 responses in LR and HR individuals have usually presented a low-probability target (go) stimulus, for which a response, e.g., button press or a mental count, was required, and a high-probability nontarget (no go) stimulus, for which no response was required. Typically, the target P300 was reduced in the HR individual compared to the LR individual. Interestingly, few studies have directly compared both go and no go P300 responses in LR and HR individuals. Such studies in other subject populations have demonstrated several phenomena. Initially, they showed that P300 can be elicited by both go and no go stimuli (Karlin et al 1970; Simson et al 1977; Pfefferbaum et al 1980, 1984, 1985; Pfefferbaum and Ford 1988; Podlesny et al 1984; Jodo and Inoue 1990; Roberts et al 1994). The studies also documented that P300 latency on no go trials was usually longer than that on go trials (Simson et al 1977; Pfefferbaum et al 1980, 1984, 1985; Pfefferbaum and Ford 1988; Podlesny et al 1984; Roberts et al 1994); however, in one study (Jodo and Inoue 1990), the subjects were tested over six sessions. Although initial no go latencies were longer than go latencies, by the last session, no go latencies were significantly shorter than both their initial values and those of the go trials. The authors attributed this reversal to a practice effect that differentially affected no go trials, and proposed that the result provided evidence for multiple P300 generators. Direct comparisons of go and no go responses have also provided information regarding their topographic distribution. In general, go responses have a parietal maximum, whereas no go responses are more anteriorly distributed, having a central or even midfrontal maximum (Simson et al 1977; Pfefferbaum et al 1980, 1984, 1985; Pfefferbaum and Ford 1988; Podlesny et al 1984; Jodo and Inoue 1990; Roberts et al 1994). These differences have been documented in several age groups (Pfefferbaum and Ford 1988), to a variety of stimuli, e.g., auditory and visual (Simson et al 1977), symbolic and linguistic (Pfefferbaum et al 1985), simple and degraded (Pfefferbaum et al 1985; Pfefferbaum and Ford 1988), to varying stimulus probabilities (Pfefferbaum and Ford 1988), and with different types of responses, e.g., button presses and counting (Pfefferbaum et al 1985).

Although there is general agreement regarding the differences in both latency and topographic distribution of go and no go responses, observations regarding P300 amplitude are more contradictory. For example, some studies reported larger P300 amplitudes on go trials (Pfefferbaum et al 1980, 1984; Pfefferbaum and Ford 1988); some, on no go trials (Karlin et al 1970; Simson et al 1977; Roberts et al 1994), whereas others found no differences (Podlesny et al 1984; Jodo and Inoue 1990). It has been suggested (Pfefferbaum et al 1985; Roberts et al 1994) that the conflicting results might be due to differences in experimental design, and may reflect the level of response preparation required by the subject on each trial. That is, when response preparation is high, no go amplitudes are generally larger than go amplitudes; when response preparation is low, the reverse is observed. Moreover, as the subject's level of response preparation is reduced, the responses appear to be more directed or guided by stimulus features.

The electrophysiological responses documented in all of the aforementioned studies reflect the recordings of scalp potentials 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) scalp potentials recorded from different subjects, experimental conditions, or time points cannot be compared because they are not derived from a common base (Wang et al 1994); b) ERP components will be altered if the placement of the reference is changed or if it is not a "quiet" reference (Nunez and Pilgreen 1991); 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) (Wang et al 1994), is a newly developed global field measure that uses the entire scalp potential (SP) field and treats potentials at different positions differently. Because scalp potentials 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. Here, the spherical spline method (Wahba 1981; Perrin et al 1987) 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, as the number of recorded potentials at the electrode sites increases, the SP or SCD field becomes a more accurate representation of the true SP or SCD field. Thus, a global field measure based on the entire interpolated SP or SCD field should more likely represent the true SP or SCD field better than one based on only finite electrode sites. SE is based on the spherical spline and the entire interpolated SCD (the surface Laplacian of scalp potential) field. 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.

In the present investigation, a visual go/no go reaction time paradigm was used to elicit the P300 component of the ERP in both LR and HR individuals. Regional response differences in P300 amplitude and latency on go and no go trials were determined both within and between groups. Determinations of SE, during both go and no go trials, were also obtained for each group; however, most importantly, we wanted to ascertain whether the P300 deficits we observed in a group of abstinent, chronic alcoholics participating in the same go/no go paradigm (Cohen et al in submission) were due to the effects of chronic alcohol abuse, or in fact, antecede its development. In that study, the alcoholics compared to the controls had reduced go and no go P300 amplitudes over the entire scalp. Moreover, whereas the controls had significantly larger go than no go amplitudes over several scalp regions, the alcoholics manifested no amplitude differences in any region. A similar pattern of deficits in the HR group would further support the hypothesis that reduced P300 amplitude may be a phenotypic marker for the development of alcoholism.

Table 1. Subject Characteristics of the Individuals in the Low-Risk (LR) and High-Risk (HR) Groups

	LR (n = 30)	HR (n = 19)
Age (years)	Mean 25.9, SD 5.87	Mean 22.9, SD 3.98
Education (years)	Mean 15.2, SD 1.94	Mean 12.9, SD 2.19
Days per month	Mean 3.69, SD 3.75	Mean 3.0, SD 3.24
Drinks per occasion	Mean 2.28, SD 1.65	Mean 2.82, SD 3.41
Drink index	Mean 9.69, SD 9.89	Mean 16.4, SD 26.1
Number of alcoholic relatives	Individuals in this group could not have any alcoholic relatives	Mean 2.58, SD 1.6

Methods

Subjects

The subjects in this study consisted of a group of men at high risk for the development of alcoholism (HR, n = 19, $\bar{X}$ = 22.9 years) and a low-risk control group (LR, n = 30, $\bar{X}$ = 25.9 years). All subjects were right-handed. LR individuals were recruited either through newspaper ads or via notices posted in the Health Science Center. In contrast, HR subjects had fathers who were undergoing treatment for alcohol dependency (DSM-III-R criteria). Initially, each prospective subject filled out a questionnaire detailing alcohol and drug use and the medical and psychiatric histories for both himself and his relatives. Participation in the study depended upon the responses to the questionnaire. Inclusion in the HR group required that at least the prospective subject's father be classified as alcohol dependent (DSM-III-R). A high incidence of alcoholism in the first and second-degree relatives of these individuals was sought for HR subjects; however, alcoholism in one's mother was cause for exclusion from the study. Prospective candidates for the LR group were rejected if any of their first- or second-degree relatives was diagnosed as alcoholic, while candidates for either group were rejected if they had major medical problems, were taking medication that affected the central nervous system, or had a history of psychiatric problems and/or drug abuse. Upon meeting the aforementioned criteria, each subject was invited to the laboratory wherein he underwent a detailed psychiatric interview (HB and BP) focusing on questions of drug and alcohol use (quantity/frequency data), and the medical and psychiatric history for both himself and his first- and second-degree relatives. Table 1 presents the demographic data for each group. A drink index (the product of the number of drinking days per month by the number of drinks per occasion) is also included. Although the index was larger in the HR group, the difference was not statistically significant because of the large variability in the measure.

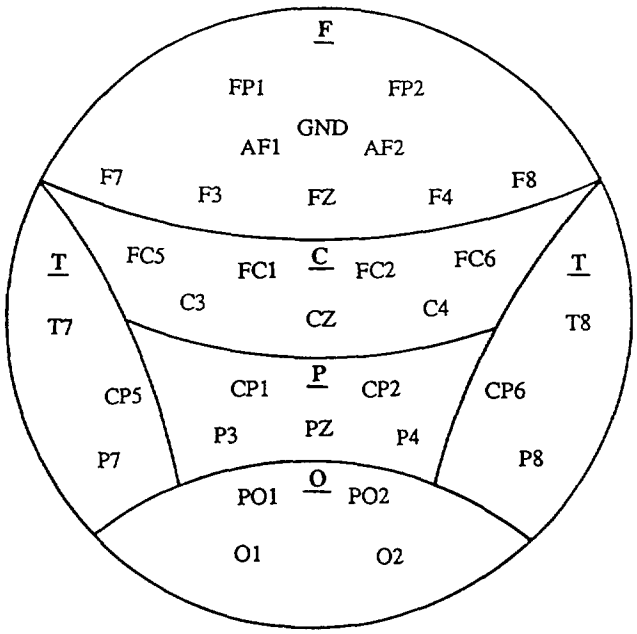

Figure 1. The recording electrode (n = 31) montage and the regional groupings (F = frontal, C = central, P = parietal, O = occipital, and T = temporal) used in the statistical analyses.

Some of the HR subjects were members of entire families participating in a national project regarding the genetics of alcoholism (COGA, Collaborative Study on the Genetics of Alcoholism). Each participating family member was interviewed with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), 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 Corporation). Each subject wore a fitted electrode cap (Electro-Cap International, Inc.) 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. Electroencephalographic (EEG) activity was amplified 20K (Sensorium EPA-2 Electrophysiology Amplifier; bandpass 0.02–50 Hz). Baseline activity was continuously sampled at a rate of 256 Hz, beginning 127 msec before stimulus onset and continuing for 2.50 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 (electromyogram, electro-oculogram, and saturation artifact >73.3 μV) were performed on-line.

The subject fixated on a target at the center of the computer monitor. He was presented with a random series of 200 visual stimuli consisting of large (p = .50; go stimuli) and small (p = .50; no go stimuli) forms of the letters T and V; the letter forms differed in size but not shape. The large and small letters subtended visual angles of 4.0 degrees and 3.2 degrees, respectively. The easier discrimination, between the large letters, determined the responding hand, whereas the more difficult discrimination, between the large and small letters, determined whether a response should be made or inhibited. The subject was told the identity of the first four stimuli to help him establish a response criterion for subsequent stimulus presentations. Stimulus duration was 105 msec, and 4- and 6-sec interstimulus intervals (ISIs) were randomly interposed between stimulus presentations. Even-numbered subjects responded to the large T and large V by button pressing with the right and left hands, respectively; odd-numbered individuals pressed with the opposite hands. When the small letters were presented, the subjects were required to inhibit any responses. Each button press terminated a clock whose onset was simultaneous with stimulus onset and recorded the response time (RT). Response speed was emphasized but not at the cost of accuracy. The subject received a maximum of 200 trials, but the experiment could be terminated after as few as 20 artifact-free trials per stimulus were acquired. The ERPs from accepted trials were automatically placed in four categories for subsequent averaging and statistical analysis; RTs were placed in two categories.

Data Analysis

For each subject, the average ERPs derived from the go and no go trials were analyzed via an automatic peak detection program that displayed the responses at all 31 electrodes; the files could then be manually edited. The P300 component was selected as the largest amplitude peak within a time window from 250 to 650 msec. Thus, each subject's data consisted of peak voltages (μV) and latencies (msec) at each of 31 electrodes for each go and no go condition.

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 Figure 1). These groupings closely

Table 2. Regional Comparisons of P300 Amplitudes (μV) on Go and No Go Trials for Low-Risk (LR, $n = 30$) and High-Risk (HR, $n = 19$) Individuals

	Go				No Go			
Region	LR		HR	Significance	LR		HR	Significance
Frontal	7.99	×	5.04	$p < .0002$	8.12	×	3.35	$p < .0005$
Central	11.7	×	8.03	$p < .02$	10.98	×	6.23	$p < .001$
Parietal	15.2	×	11.71	$p < .04$	12.44	×	9.74	$p < .009$
Occipital	10.7	×	9.33	$p < .0001$	8.22	×	7.80	$p < .0001$
Temporal	8.36	×	5.82	$p < .02$	7.27	×	5.05	$p < .0002$

corresponded to the underlying scalp regions and were used in both within- and between-groups regional comparisons.

Next, both the P300 amplitude and latency data were normalized (McCarthy and Woods 1985); the normalized data were then used in the subsequent statistical comparisons.

Within-group multivariate analyses of variance (MANOVAs, SAS v. 6.09) were used to assess differences between go and no go P300 amplitudes and latencies, in reach region, for both the LR and HR groups. Between-groups MANOVAs, were then used to assess group differences in both go and no go P300 amplitudes and latencies in each region. For each group, SE magnitudes were compared on both go and no go trials. Lastly, independent group t tests were used to measure group differences in RTs to go stimuli, and in error rates, i.e., missed go stimuli and button presses to no go stimuli.

Results

Response Time

Initially, comparisons were made between left-hand (LH) and right-hand (RH) RTs for individuals in both the LR and HR groups. Neither group demonstrated a significant laterality difference. Between-group comparisons showed that RTs in the LR group were significantly faster than those in the HR group for both LH (LR, $\bar{X} = 580.8$; HR, $\bar{X} = 737.8$; $p < .0001$) and RH (LR, $\bar{X} = 593.6$; HR, $\bar{X} = 762.8$; $p < .0001$) responses.

P300 Responses—within-Group Comparisons

Initially, for both the LR and HR groups, within-group MANOVAs, were used to determine if any response differences existed between the two types of go trials (large T and large V) and the two types of no go trials (small T and small V). Because neither group manifested a significant amplitude or latency difference in either comparison, the two types of go responses and the two types of no go responses were merged for subsequent within- and between-group analyses.

Then, for each group, comparisons were made in each region, between the merged, go responses and the merged, no go responses (both amplitudes and latencies). For the LR group, P300 amplitudes on go trials were significantly larger than those on no go trials in the central ($p < .03$), parietal ($p < .04$), and temporal ($p < .04$) regions. In contrast, the HR group manifested no differences between go and no go P300 amplitudes, in any region. For both groups, comparisons between merged go and no go P300 latencies revealed no significant differences in any region.

P300 Responses—between-Group Comparisons

Between-group MANOVAs were used to compare P300 amplitudes and latencies on both go and no go trials in each region. The results demonstrated that LR individuals, compared to HR individuals, had significantly larger go trial and no go trial amplitudes in each of the five regions. In contrast, there were no significant go or no go latency differences in any region. Table 2 presents, for both the LR and HR groups, the mean amplitudes for go and no go trials, in each region.

Figures 2 and 3 present, at each of the 31 electrodes, the mean P300 waveforms for the LR ($n = 30$) and HR ($n = 19$) individuals on go trials (Figure 2) and no go trials (Figure 3). It is apparent that there is little difference in the topographic distribution of go and no go responses.

Surface Energy

Determinations of SE paralleled the measures of P300 amplitude, and indicated greater SE magnitudes in the LR group, during both go and no go trials.

Figure 4 presents surface energy (SE) determined on go trials, for both the low-risk (LR; left) and high-risk (HR; right) groups. The early SE peak, occurring between 150 and 175 msec, reflects stimulus encoding and perception. In the LR group compared to the HR group, its magnitude is ca. 1.6 times greater and its latency is ca. 25 msec earlier.

The later SE peak, occurring between 400 and 450 msec, corresponds to the period of maximum P300 ampli-

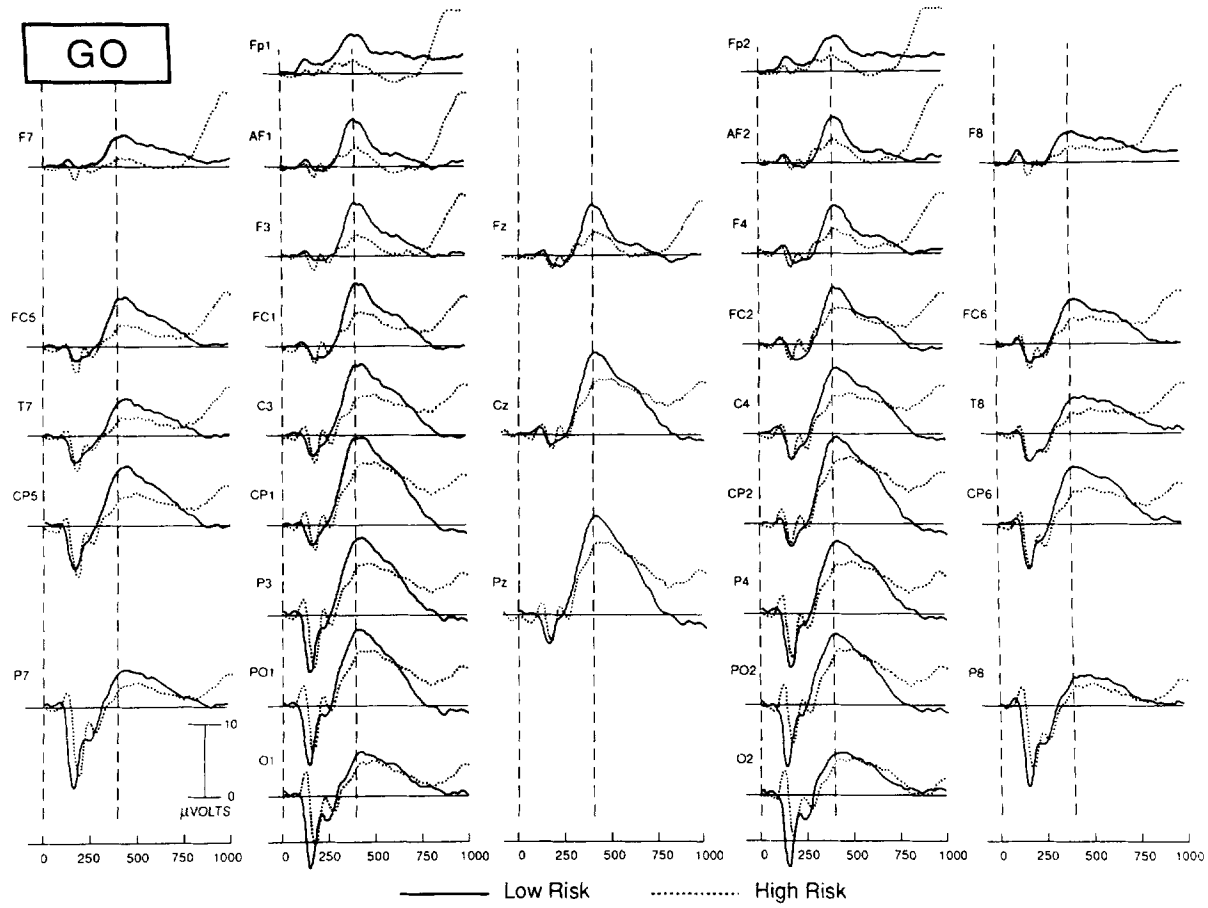

Figure 2. Mean P300 waveforms elicited by go stimuli at all 31 electrodes, for both low-risk (solid line) and high-risk (dashed line) individuals.

tude. In the LR group compared to the HR group, its magnitude is ca. 1.7 times greater and its latency ca. 25–30 msec earlier.

Error Rates

Comparisons of error rates between the LR and HR individuals indicated that there were no group differences either in the number of missed go stimuli, or button presses to no go stimuli.

Discussion

The present investigation demonstrates that during the performance of a simple information-processing paradigm there are widespread, significant differences in P300 morphology between LR and HR individuals. LR subjects, compared to HR subjects, had significantly larger P300 amplitudes on both go trials and no go trials, in each of the five scalp regions; however, comparisons of P300 latencies on go and no go trials evidenced no group differences in any region. Also documented was the fact that in the LR group, P300 amplitudes on go trials were significantly larger than those on no go trials, in the central, parietal, and temporal regions; however, in the HR group, no differences between go and no go response amplitudes were observed in any region. Determinations of SE magnitudes paralleled the measures of P300 amplitude and also revealed deficits in the HR group compared to the LR group during both go and no go trials. Lastly, although RT comparisons showed the LR group to be significantly faster than the HR group with both left and right hands, error rate comparisons, i.e., missed go stimuli and button presses to no go stimuli, revealed no group differences.

Reduced P300 amplitude in HR individuals has been documented in numerous studies. Since Begleiter et al (1984) first demonstrated that P300 amplitude is reduced in the unaffected male children (ages 7–13) of chronic alcoholics without the administration of ethanol, subsequent studies in the same laboratory (Begleiter et al 1987; Porjesz and Begleiter 1990, 1993; Ramachandran et al

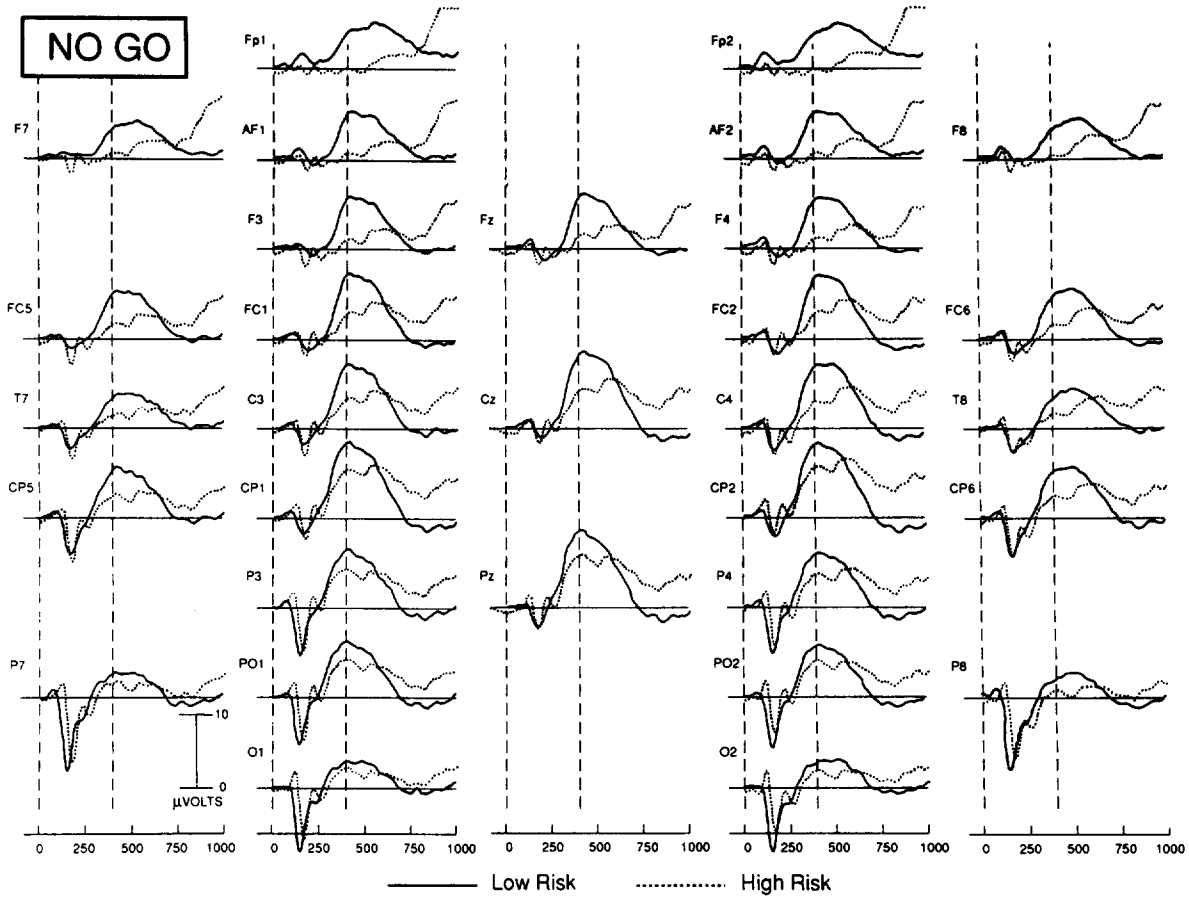

Figure 3. Mean P300 waveforms elicited by no go stimuli at all 31 electrodes, for both low-risk (solid line) and high-risk (dashed line) individuals.

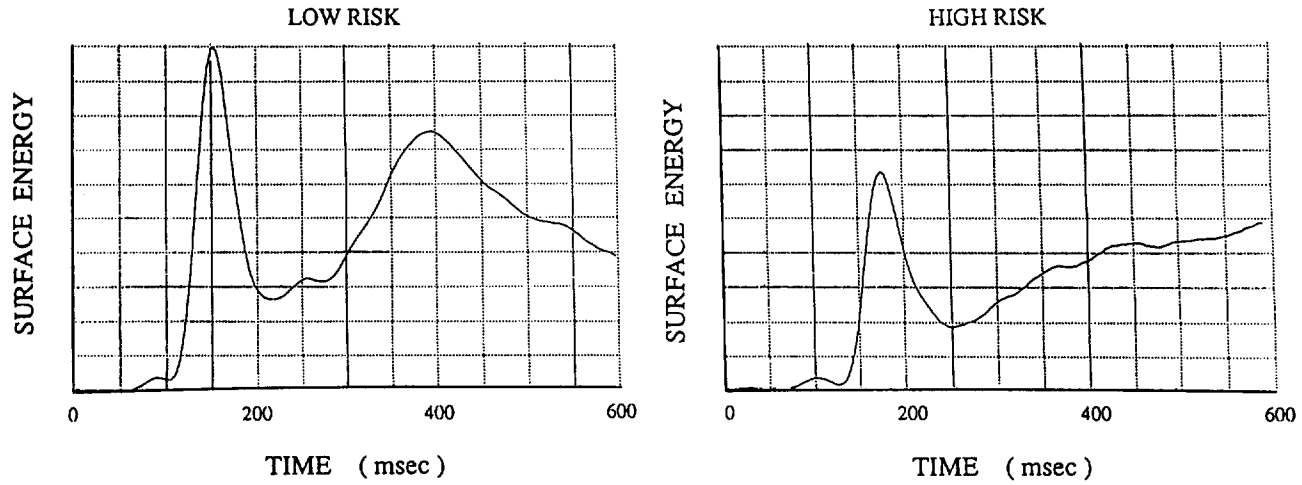

Figure 4. Surface energy, analogous to the bending energy of the SP field, measured during go trials, is presented as a function of time (msec) for both low-risk (LR) (left) and high-risk (HR) (right) individuals. In the LR group compared to the HR group, magnitudes of both the early (150–175 msec) and late (400–450 msec) SE peaks are ca. 1.7 and 1.6 times larger, respectively. The later surface energy peak corresponds to the interval of maximum P300 amplitude. Each time division is 50 msec.

1996) and others (O'Connor et al 1986, 1987; Hill et al 1988; Whipple et al 1988, 1991; Noble 1990; Berman et al 1993; Hill 1993; and Steinhauer) have replicated this finding. This suggests that reduced P300 amplitude is a highly heritable trait that antecedes the development of alcoholism and may be considered as a phenotypic marker (Begleiter and Porjesz 1988; Pfefferbaum et al 1991; Berman et al 1993; Polich et al 1994). Support for this hypothesis comes from several sources. For example, Pfefferbaum et al (1991), conducted a path analysis of family history negative and family history positive alcoholics and concluded that family history was more important than drinking history in accounting for the P300 deficit in alcoholics. Polich et al (1994), in a meta-analysis of individuals at low risk and high risk for the development of alcoholism, demonstrated that individuals with a positive family history of alcoholism manifested smaller P300 amplitudes than individuals with a negative family history. Cohen et al (1995), using an auditory oddball paradigm, documented that whereas P300 amplitudes in low-density alcoholics (no alcoholic relatives/individual) resembled those in control individuals, in contrast, high-density alcoholics (4.4 alcoholic relatives/individual), compared to controls, had significantly reduced P300 amplitudes over the entire scalp.

Together, these studies suggest that genetic factors may underlie the group differences in P300 amplitude. Evidence for a possible genetic contribution to both EEG and ERP morphology derives from investigations of alcoholics and their relatives and from twin studies (Propping 1977; Propping et al 1981; Polich and Burns 1987; O'Connor et al 1994). These studies have documented that: 1) monozygotic (MZ) twins compared to dizygotic (DZ) twins had greater similarities in both baseline EEG activity and the EEG response to an ethanol challenge; 2) alcoholics and their nonalcoholic first-degree relatives manifested more similar EEG variants than did alcoholics and matched controls (Propping 1977; Propping et al 1981); 3) both P300 amplitudes and latencies were significantly correlated in MZ twins as compared to control pairs (Polich and Burns 1987); and 4) there is significant heritability of P300 amplitude, latency, and wave shape, with responses of MZ twin pairs more similar than those of DZ twin pairs (O'Connor et al 1994).

Surface Energy

By using a 31-electrode recording montage we were able to demonstrate that the deficit in P300 amplitude manifested by the HR group, on both go and no go trials, was not restricted to central and parietal regions where P300 is most prominent, but was evidenced over the entire scalp, a larger extent than has typically been described. The reduction in P300 amplitude during both go and no go trials was paralleled by decreases in SE, a reference-free global field measure, which uses the entire scalp potential field and treats potentials at different positions differently. These decreases in SE magnitude during the period of maximum P300 amplitude (400–450 msec) are similar to the deficits we observed in two studies of abstinent, chronic alcoholics (Cohen et al 1995, in submission). In the first (Cohen et al 1995), the subjects engaged in an auditory oddball paradigm, whereas in the second (Cohen et al in submission), they participated in the same go/no go paradigm used in the present investigation. In the present study it should be noted that in the HR group compared to the LR group, the early SE peak (150–175 msec) was both reduced in magnitude and later in latency. The decrease in SE magnitude appears to correspond to a decrease in N1 amplitude, ca. 150 msec, evidenced at numerous recording sites (see Figure 2). We believe that the early SE peak reflects processes including stimulus detection, activation of afferent pathways, and stimulus encoding. As such, the deficits manifested by the HR group suggest that these mechanisms are in some way compromised.

Inhibition

Currently, there is evidence suggesting that P300 reflects the transient activation of inhibitory processes over widespread cortical regions (Desmedt 1980; Verleger 1988; Birbaumer et al 1990; Rockstroh et al 1992; Roberts et al 1994; Schupp et al 1994; Stenberg 1994). The proposed relationship between positive-going cortical activity and the activation of inhibitory processes derives from several studies. For example, both Woodward et al (1991) and Rockstroh et al (1992) observed that during the performance of an auditory oddball paradigm, reaction times to probe stimuli increased when the probes were presented during the 300–700-msec interval following maximally positive P300 responses. Similarly, Schupp et al (1994) reported that in the period after no go P300 responses, startle reflex magnitudes decreased, whereas positive-going EEG components increased. The authors interpreted this response pattern to indicate the activation of inhibitory processes. Born et al (1982) demonstrated that delayed response tasks were solved more slowly when presented contingent upon positive slow potential shifts than when presented contingent upon frontal negative shifts. Lastly, evidence from extracellular recordings indicates that discharge rates may decrease during the presentation of cognitive stimuli (Bechtereva et al 1992), although Halgren et al (1980) suggested it may be difficult to correlate single neuron discharge patterns with cognitive task performance.

Neural Generators of P300

The observation that P300 can be recorded over the entire scalp, with relatively small regional differences in latencies, suggests that it may not derive from a single neural generator whose activity is volume conducted through the central nervous system (Johnson 1993). Rather, P300 may be generated by multiple sources, both subcortical and cortical, with the former having diffuse cortical terminations. Included among the possible sources are the anterior hippocampus (Halgren et al 1980), basal forebrain (Harrison et al 1988), thalamus (Yingling and Hosobuchi 1984; Roberts et al 1994), parietotemporal cortex (Knight et al 1989), and frontal lobe (Baudena et al 1995). Recently, Roberts et al (1994) proposed how the reticular nucleus of the thalamus might be involved in P300 generation. They suggested that during the processing of relevant stimuli, the reticular nucleus may act via lateral inhibitory mechanisms to differentially inhibit thalamocortical systems not activated by the stimulus. Thus, in a manner similar to that by which lateral inhibition acts to sharpen stimulus detection in both the visual and somatosensory systems, the inhibition of cortical regions not involved in the ongoing task may also act to enhance information processing (Birbaumer et al 1990; Stenberg 1994); however, because P300 amplitude is reduced in HR individuals, it is likely that there is a deficit in the inhibitory mechanisms and/or pathways underlying its generation.

Go/No Go Amplitude Differences

In the present investigation, P300 amplitudes in the LR group were significantly larger on go trials than on no go trials in the central, parietal, and temporal regions. In contrast, the HR group manifested no differences between go and no go amplitudes in any region. These findings in the LR group replicate those of Pfefferbaum et al (1980, 1984, 1985; Pfefferbaum and Ford 1988) and support the observation (Pfefferbaum et al 1985; Roberts et al 1994) that the relationship between go and no go P300 amplitudes is related to the subject's level of response preparation. To some extent, the amount of response preparation required on each trial is a function of the experimental design. In general, when the subject must maintain a high preparatory level, no go P300 responses are larger than go P300 responses. In contrast, when only a low level of preparation need be maintained, go trial amplitudes are usually larger than those generated on no go trials. For example, both Simson et al (1977) and Roberts et al (1994) obtained larger amplitudes on no go trials. In the first study (Simson et al 1977), the subject received paired stimuli that consisted of a warning stimulus, S1, and an imperative stimulus, S2; however, because the S1–S2 interval was only 1 sec in duration, and because the intertrial interval was 8 sec, it is unlikely that the subject's preparatory level would be exceedingly high. The augmented no go responses were attributed to a contribution from a slow negativity, the contingent negative variation (CNV), that developed during the S1–S2 preparatory interval. When S2 signaled no go, CNV resolution occurred quickly, and an augmented P300 was produced; however, when S2 signaled go, the CNV, whose later components are related to response preparation (Rohrbaugh et al 1976), continued until the response was made; the persistence of CNV produced a go P300 response whose amplitude was reduced. Further, when the authors subtracted the CNV contribution to the no go response at each electrode, the no go response then resembled the go response both in amplitude and topography. In the second study (Roberts et al 1994), the authors used a continuous performance task in which stimuli were presented continuously every two sec. With this type of experimental design, the subject must maintain a much higher state of response preparedness than was required in Simson et al. (1977). As a consequence, the authors observed no go P300 amplitudes as large as 41 μV at the Cz electrode; these magnitudes were more than twice those (15 μV) reported by Simson et al (1977); however, in contrast to Simson et al (1977), when Roberts et al (1994) subtracted the CNV contribution to the no go response at each electrode, neither its amplitude nor its topography were significantly altered.

In the present investigation, response preparation was kept low both by omitting a warning stimulus and by using rather long intertrial intervals of 4 and 6 sec. As a consequence, the subject may have adopted a strategy in which he did not so much prepare to respond, as concentrate on discriminating the specific stimulus features that determined either his responding hand (large T or large V) or his decision to respond or inhibit his response (letter size). Pfefferbaum and Ford (1988) noted that response inhibition may reflect how well the subject translates the no go instruction to the nontarget (no go) stimulus. To maximize the information contained in each stimulus Pfefferbaum et al (1985; Pfefferbaum and Ford 1988) actually used the words PUSH and WAIT as go and no go stimuli, respectively.

An alternative explanation for the difference in go and no go P300 amplitudes derives from the evidence that there are multiple P300 generators. The previously described studies that have localized P300 generation to multiple cortical and subcortical sites, as well as the study by Jodo and Inoue (1990), which demonstrated differential effects of practice on go and no go P300 latencies, suggest the possibility that in the present investigation, go and no go P300s may reflect the activity of independent genera-

tors conceivably operating through similar inhibitory mechanisms.

In conclusion, the results of our study indicate that HR individuals differ electrophysiologically from LR individuals. These differences are manifested as widespread reductions in P300 amplitude, and are observed during both response production and inhibition during the performance of a visual information processing paradigm. The P300 deficits suggest a deficiency in an inhibitory mechanism proposed to underlie P300 generation. Interestingly, the pattern of within- and between-group responses in the HR group was the same as that evidenced by a group of abstinent, chronic alcoholics who participated in the same paradigm. Thus, the amplitude deficit may reflect the influence of genetic factors, precede the onset of alcoholism, and function as a phenotypic marker for its development.

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