Auditory P3a Assessment of Male Alcoholics

Michio Hada, Bernice Porjesz, Henri Begleiter, and John Polich

Background: *P3a amplitude differences between alcoholic and control groups have not been well defined. Because event-related potential (ERP) differences between these groups appear to be influenced by task difficulty, the present study employed a new auditory ERP paradigm, in which target/standard tone discriminability was difficult, with infrequent nontarget stimuli used to elicit the P3a.*

Methods: *A total of* n = *27 male alcoholics and* n = *25 male controls were assessed using a three-tone discrimination paradigm, in which the discriminability between the target and standard was difficult, with easily discriminable infrequent nontarget tones also presented. A P3a component with a centro-frontal maximum to the rare nontargets and a P3b with a parietal maximum amplitude to the target stimulus were obtained. Current Source Density (CSD) maps were derived from the potential data and employed to assay topographical differences between subject groups.*

Results: *Alcoholics produced smaller P3a amplitudes than control subjects to the rare nontargets with no peak latency differences observed. The most prominent current sources are apparent more anteriorly for the nontarget compared to the target stimulus in both groups. There were more sources and sinks in the alcoholics than in the control subjects for P3a. A bootstrap analysis method showed that P3a CSD maps evinced distinct topographic distributions between alcoholics and control subjects in all brain regions.*

Conclusions: *The lower P3a amplitude and weaker sources in alcoholics coupled with less topographic specificity in their CSD maps, suggests disorganized inefficient brain functioning. This global electrophysiological pattern suggests cortical disinhibition perhaps reflecting underlying CNS hyperexcitability in alcoholics.* Biol Psychiatry 2000;48:276–286 © *2000 Society of Biological Psychiatry*

Key Words: P300, P3a, P3b, alcoholics, auditory event-related potential, Current Source Density, frontal cortex, cortical disinhibition

Introduction

Event-related brain potentials (ERPs) can be used to assess the cognitive deficits in alcoholism by providing spatial and temporal assays of neural function from scalp recordings. In particular, the P300 ERP component is often employed, because it is a sensitive index of stimulus evaluation and attentional allocation processes (Donchin et al 1986; Polich 1986). The P300 is often elicited using a simple discrimination task, the so-called "oddball" paradigm, in which two stimuli are presented in a random series with one of the two occurring relatively infrequently (i.e., the oddball). The subject is required to distinguish between the two tones by responding to the target (e.g., mentally counting, pressing a button, etc.) and not responding to the standard (Duncan-Johnson and Donchin 1977; Polich 1986, 1987); a variety of psychological factors affect P300 amplitude and latency, such as target probability, stimulus size/intensity, and ease of standard/target discriminability (Johnson 1988; Polich 1998).

An important aspect of P300 is that intrusive or "novel" stimuli (e.g., dog barks, abstract color forms, etc.) can produce an earlier, positive potential called "P3a" that appears to be distinct from the later P300 or "P3b" peak (Squires et al 1975). P3a is typically larger in amplitude than the P3b over the frontal and central electrode sites and is thought to reflect an alerting process that originates in the frontal cortex (Courchesne et al 1975; Ebmeier et al 1995; Friedman and Simpson 1994; Friedman et al 1993; Knight 1984). Recent reports, however, indicate that P3a amplitude is directly affected by the discrimination difficulty between the target and standard stimuli and not by novel stimulus characteristics (Comerchero and Polich 1998, 1999; Katayama and Polich 1998). These studies suggest that the P3a reflects attentional processes related to signal evaluation, because it is elicited by rare deviant stimuli presented when selective attention is engaged in the absence of a response, appears to originate from the frontal lobe, and readily habituates (Knight 1996; Potts et

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al 1996). When memory processes store the incoming stimulus information, the central/parietal P3b is generated (Knight 1990; McCarthy et al 1997). Thus, P3a reflects the initial response to an incoming signal, and P3b indexes the attentional and mnestic operations invoked to process the stimulus.

Alcoholism, P3a, and P3b

P3b amplitude is smaller in abstinent alcoholics compared to control subjects (Pfefferbaum et al 1991, Porjesz et al 1980, 1987); it is also reduced in long-term abstinent alcoholics (for reviews, see Begleiter and Porjesz 1995; Porjesz and Begleiter, 1996). Recent evidence suggests that callosal size may be a factor; the size of callosal fiber tracts are correlated with P300 in normal subjects (Alexander and Polich 1995; Polich and Hoffman 1998), and smaller corpus callosal areas have been observed in alcoholics based on magnetic resonance imaging (MRI) recordings (Pfefferbaum et al 1996). These results suggest that cognitive impairment in alcoholics (Eckardt et al 1988; Goldman and Goldman 1988; Sanders et al 1989; Tamkin and Dolenz 1990; Tarbox et al 1986) may stem from fundamental neuroanatomical variables that contribute to P300 generation.

The majority of ERP studies in alcoholics have used paradigms that elicit only the P3b, with the general finding that amplitude deficits in alcoholics are more pronounced in visual stimulus tasks and are less consistently observed in easy auditory paradigms (e.g., Porjesz et al 1980, 1987). The few reports using P3a paradigms to evaluate alcoholism have obtained mixed results: Alcoholics produced smaller P3a amplitudes in an auditory passive paradigm (Pfefferbaum et al 1991; Realmuto et al 1993), but no group amplitude differences were found for an easy novel visual stimulus paradigm (Biggins et al 1995). In contrast, a difficult target/standard visual discrimination task did obtain substantial P3a deficits to easy-to-detect rare nontargets in alcoholics compared to control subjects, with major group differences observed over frontal areas (Rodriguez-Holguín et al 1999). Taken together, these results indicate that P3a deficits in alcoholics may exist, but the nature of these effects is not yet clear.

P3 and Gender Difference

Given that the P3a reflects initial signal evaluation and the P3b reflects subsequent attention resource and memory processes that store stimulus information (Knight 1990; Polich and Margala 1997), it is reasonable to suppose that communication between the frontal hemispheres would occur via the corpus callosum (cf. Baudena et al 1995; Satomi et al 1995). Following this inter-hemispheric communication, parietal attention, activation, and subsequent hippocampal operations would be engaged to incorporate the incoming stimulus information into memory (Halgren et al 1995a, 1995b; Posner 1992). Indeed, individuals with inherently larger callosal fiber tracts, such as left- compared to right-handers (Driesen and Raz 1995), demonstrate larger P3b amplitudes, perhaps because of increased inter-hemispheric communication (Alexander and Polich 1995, 1997; Polich and Hoffman 1998). Similarly, several researchers found gender differences in the corpus callosum size in postmortem morphological studies (Witelson 1989; Steinmetz et al 1995), and gender differences have been observed in P3b studies of normal control subjects (Johnson 1989; Polich et al 1990; Segalowitz and Barnes 1993; van Beijsterveldt et al 1998). Although the studies of gender differences in P3a have not been conducted, it is suggested that because P3a reflects initial signal evaluation during communication between the frontal hemispheres via corpus callosum, female subjects who have larger corpus callosums would manifest larger P3a than males. Thus, in the present study, we tested only male subjects, thus excluding the possible gender effect on P3a.

Table 1. Subject Group Statistical (Mean and SD), Demographic, and Clinical Information

	Alcoholics	Control subjects
Sample size	27	25
Age (years)	37.0 (5.1)[a]	28.3 (6.2)
Education (years)	12.4 (2.2)	13.6 (2.2)
Drinking onset age (year)	15.8 (3.7)[a]	Not applicable
Drinking days/month	12.5 (2.2)[a]	1.9 (2.0)
Drinks/occasion	6.2 (6.8)[a]	2.5 (2.3)

[a] $p < .05$.

Present Study

A critical factor for delineating P3a amplitude effects in alcoholics appears to be the nature and modality of the discrimination task. The present study was therefore conducted to ascertain whether P3a from a difficult auditory three-tone paradigm would be affected by alcoholism. This issue is important, because it is suggested that P3a reflects frontal lobe function. Alcoholics and control subjects were assessed, and both ERP and Current Source Density (CSD) analyses were performed to define topographic as well as possible source/sink group differences.

Methods and Materials

Subjects

Table 1 presents demographic descriptions of the alcoholic and control subjects, all of whom were right-handed and male. All subjects provided informed consent and received pecuniary remuneration for their participation. Exclusionary criteria for

both groups included major medical problems, a current requirement for central nervous system (CNS)-sensitive medication, and history of psychiatric problems. None of the subjects in either group met DSM III-R criteria for drug dependence; however, 39% of the alcoholics met criteria for polysubstance abuse secondary to alcoholism. Alcoholics met both DSM-III-R alcohol dependence and Feighner "definite" criteria to define alcoholism. Alcoholics were undergoing 30 days of alcoholism treatment at a local hospital. Some individuals in this program were on a regimen that included vitamin and nutritional therapy, and all were monitored closely for any signs of drug and/or alcohol abuse. Alcoholics were assessed with the ERP paradigm on their 28th day in the program, or as close as possible to their release. Exclusionary criteria included history of psychiatric disorder, intravenous drug use, treatment medication (e.g., Antabuse), psycho- or CNS-active drugs, seizures unrelated to withdrawal, retardation, hearing, or visual impairments and liver damage (e.g., cirrhosis). Control subjects were recruited with newspaper advertisements or notices posted in the State University of New York Health Science Center. The initial screening required completion of a questionnaire detailing alcohol/drug use and the medical and psychiatric histories for himself and his relatives. Exclusion criteria included specific responses about alcohol/drug use and that none of the control candidates' first- or second-degree relatives were diagnosed alcoholics.

After the initial screening, subjects came to the laboratory and were given a detailed psychiatric interview focusing on questions of drug and alcohol use (quantity/frequency), with the medical and psychiatric histories for himself and first- and second-degree relatives obtained. Some subjects (both alcoholic and control) were members of families participating in a large-scale study on the genetics of alcoholism (Collaborative Study on the Genetics of Alcoholism). In this case, each participating family member was interviewed with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), which uses both DSM-III-R alcohol dependence and Feighner criteria to define alcoholism (Bucholz et al 1994). Interviews with family members were used to document the family history information. Subjects were required to undergo a breath analyzer test, and a urine screen was performed on the day of testing. Subjects with positive alcohol or drug screens were excluded. None of the subjects in the sample were in withdrawal on the day of testing. Caffeine and tobacco users were not excluded.

ERP Paradigm and Recording

The subject was seated in a reclining chair in a sound-attenuated shielded room and fixated on the center of a computer screen 1 m in front of him. The subject was presented with 350 binaural tones through headphones at 103 dB SPL (10 msec rise/fall, 40 msec plateau) and an inter-stimulus interval of 1.5 sec, with 270 standard (1630 Hz), 35 target (1530 Hz), and 35 nontarget (670 Hz) stimuli. The target and standard stimuli were difficult to discriminate from each other, but the nontarget stimulus was readily perceived. The experiment concluded when all 350 stimuli had been presented.

The subjects were instructed that they would hear high, medium, and low tones and to press a button on a modified computer mouse as quickly as possible after hearing the medium tone. Response time (RT) and error rate were recorded, with subjects told that speed was important but not at the cost of accuracy. Trials with RTs $>$ 1000 msec were rejected. Practice trials were presented initially with 18 stimuli that included repeated patterns of standard, target, and nontarget.

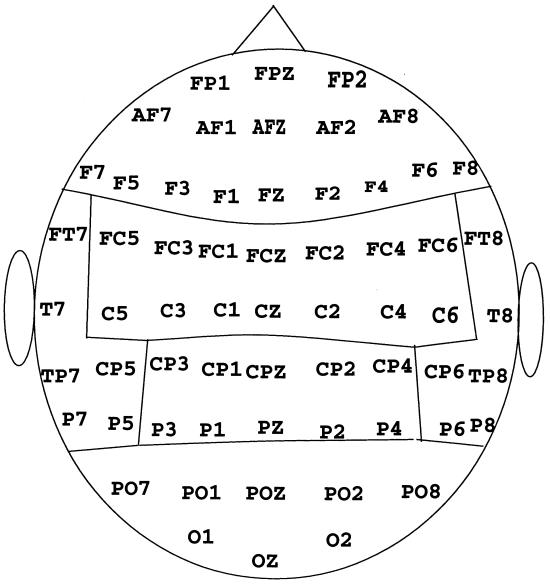

Figure 1. Schematic illustration of the electrode montage and six regional groupings (frontal, central, parietal, occipital, right temporal, left temporal) used in the statistical analyses of the event-related brain potential and current source density data.

An electrode cap with 61 electrodes (ECI, Electrocap International, Eaton, OH) was used such that the entire 10–20 system and 41 additional sites were recorded as follows: Fpz, Afz, Af1, Af2, Af7, Af8, F1, F2, F5, F6, Fcz, Fc1, Fc2, Fc3, Fc4, Fc5, Fc6, FT7, FT8, C1, C2, C5, C6, Cpz, Cp1, Cp2, Cp3, Cp4, Cp5, Cp6, Tp7, Tp8, P1, P2, P5, P6, POz, PO1, PO2, PO7, and PO8 (Electrode Position Nomenclature, American Electroencephalographic Society 1991). Scalp electrodes were referred to the nose, with a ground electrode on the forehead, and the impedances below 5 kohms. Both vertical and horizontal eye movements were monitored with electrodes that were placed supraorbitally and at the outer canthus of the right eye. The signals were amplified with a gain of 10,000 by Ep-A2 amplifiers (Sensorium, Charlotte, VT), with a 0.02–50 Hz bandpass interfaced to a Concurrent 55/50 computer. The sampling rate was 256 Hz, with a 187.5 msec prestimulus baseline and epoch length of 1323 msec. Digital filtering (16 Hz low-pass) and artifact rejection (electromyogram, electro-oculogram, saturation $>$73.3 μV) were performed off-line.

ERP Data Analysis

The P3a and P3b components were defined as the largest positive-peak within a latency window of 250–450 msec. Peak amplitude was measured relative to the prestimulus baseline, and peak latency was measured from the time of stimulus onset.

Figure 1 illustrates the regional grouping of component amplitudes that were employed for statistical analyses, which consisted of frontal, central, parietal, occipital, and left and right temporal regions. The mean amplitudes across electrodes within each region were employed as the dependent amplitude measures. Multivariate analyses of covariance (MANCOVA) were performed for the P3a comparisons between the two groups, with subject age used as a covariate even though the small group age difference was very unlikely to affect either amplitude or latency measures (cf., Anderer et al 1997; Polich 1997). For intragroup P3a and P3b assessment, multivariate analyses of variance (MANOVA) were employed.

Current Source Density Analysis

Scalp ERPs can reflect the average activity of multiple neural sources recorded at a distance so that they are neither reference free nor independent of volume conductor effects. These limitations imply that ERP components will be altered if the recording reference is noisy or changed, such that "spatial smearing" of potential amplitudes can occur as a consequence of differential volume conduction (Nunez and Pilgreen 1991). CSD maps were therefore constructed based on the ERP amplitudes using the grand mean derived from Laplacian transformations (Gevins et al 1991; Law 1991; Law and Nunez 1991; Perrin et al 1987a, 1987b). This method yields an accurate estimate of the local current density, because it acts as a spatial filter that enhances local over distant sources. Hence, CSD is a viable index for both current sources and sinks, because it reflects cortical activity such that positive current density corresponds to a source region where a local radial current is flowing through the skull into the scalp, and negative current density corresponds to current flow into the skull. Topographic CSD maps were constructed for both groups using the nontarget amplitudes measured at the average peak latency (Wang et al 1994).

For analysis purposes, CSD maps were additionally obtained for both subject groups using the bootstrap method (Srebro 1996). All the amplitude data from the two groups were pooled and treated as if they were one group and then randomly assigned to new groups, such that three pools with n subjects each were created: 1) randomly selected only from controls; 2) randomly selected only from alcoholics; 3) randomly selected from both groups. If the CSD scalp field topography shapes between the control and alcoholic groups are different, the correlation coefficient (Pearson's r) computed between groups using the CSD value across electrodes within each of the topographic regions defined in Figure 1 will be zero. If the CSD scalp topography shapes are not different, the correlation coefficient will be significantly greater than zero. By repeating the random selection procedure 200 times, an empirical estimate was obtained for the variability associated with the difference between the two correlations (one that keeps the groups separate, "alcoholic vs. control," and one that pairs the groups randomly, "random-1 vs. random-2"). The Fisher's Z transformation of R was applied to the correlations obtained from each sampling, and the Z values were assessed using a t test.

Results

Task Performance

The mean percentage of errors was 1.9%, with no statistically reliable group differences found. Alcoholics responded significantly slower than controls (529.5 vs. 518.5 msec), with $t(51) = 4.2$, $p < .0001$. Given the low error rates and only a 10 msec group difference, however, it is reasonable to conclude that task performance was equitable for each group.

ERP Analyses

Figures 2a and 2b illustrate the grand average ERPs for rare target and nontarget at nine key electrodes representing midline (Fz, Cz, Pz), left (F3, C3, P3), and right (F4, C4, P4) sites for the control subjects and alcoholics, respectively. Table 2 indicates the mean P3a amplitude in both groups at these nine key electrode sites. Figure 3 illustrates the mean P300 amplitudes from the rare nontarget (P3a) stimulus condition for each subject group.

Intra-Group P3a and P3b Assessment

The P300 data from the rare nontarget (P3a) and target (P3b) were analyzed separately for each group using a two-factor (2 stimulus types $\times$ 4 electrodes) MANOVA to determine whether the two groups differed with respect to whether the three-stimulus paradigm produced similar P3a and P3b outcomes in each subject group. *Control* subjects evinced significantly larger overall P3a than P3b amplitudes, $F(1,24) = 26.2$, $p < .001$, and increasing amplitudes from the frontal to parietal/occipital electrodes, $F(3,72) = 3.7$, $p < .001$. Amplitudes were larger frontally and centrally for the nontarget compared to the parietal maximum for the target stimuli to produce a significant stimulus type $\times$ electrode interaction, $F(3,72) = 4.2$, $p < .01$. P3a had consistently shorter peak latency than P3b, $F(1,24) = 167.1$, $p < .001$, with no other reliable outcomes obtained ($p > .50$ in all cases). *Alcoholic* subjects produced larger P3a compared to P3b amplitudes, $F(1,26) = 7.1$, $p < .01$, similar increases across the midline, $F(3,78) = 3.7$, $p < .001$, and stimulus type $\times$ electrode interaction, $F(3,78) = 3.0$, $p < .05$. P3a latency was again shorter than P3b, $F(1,26) = 206.5$, $p < .001$, with no other reliable outcomes obtained ($p > .75$ in all cases). In sum, both subject groups produced similar P3a and P3b amplitude and latency patterns.

Nontarget P3a

A comparison of the ages of the alcoholics and control subjects revealed a statistically significant difference (Stu-

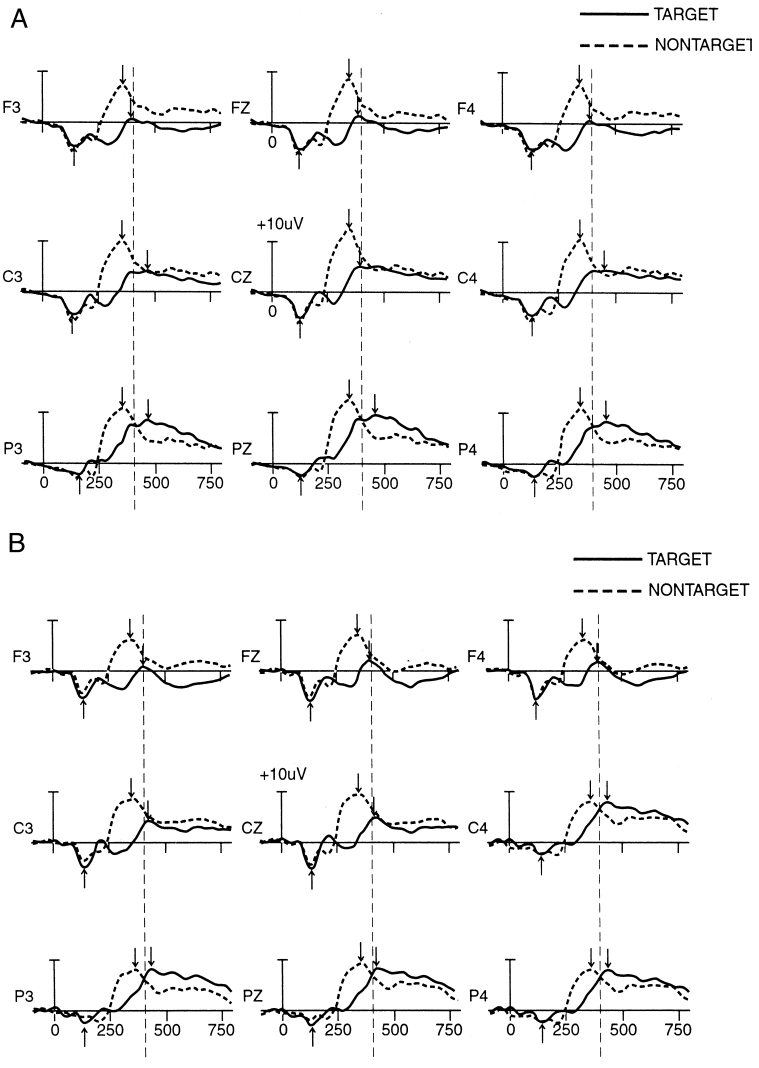

Figure 2. **(A)** Control subjects ($n = 25$) event-related potential (ERP) grand averages for target, nontarget, and standard stimuli for nine electrode sites. **(B)** Alcoholic subjects ($n = 27$) ERP grand averages for target, nontarget, and standard stimuli for nine electrode sites.

dents t test $p < .0001$). The adequacy of a covariate for age was statistically evaluated. A simple regression analysis for age was performed to evaluate the effects of age on both amplitude and latency of rare nontarget P3. For amplitude, $r = .4$, $p < .001$ in alcoholics, $r = .11$, $p < .001$ in control subjects over all regions. In the frontal region, $r = 0.13$, $p < .01$ in alcoholics, $r = 0.17$, $p < .01$ in control subjects. In the other regions, the rare nontarget amplitudes were not significantly regressed on age. These results indicated that the use of a covariate for age was valid for amplitude over all regions and frontal region. For latency, over all regions $r = .14$, $F = 4.8$, $p < .05$ in alcoholics, $r = .2$, $p < .01$ in control subjects. In the other regions, the rare nontarget latency was not significantly regressed on age. P3a amplitude from the nontarget stimulus was assessed using a two-factor (2 groups $\times$ 6 regions) MANCOVA. Control subjects demonstrated larger amplitudes overall than alcoholics, $F(1,51) = 10.2$, $p < .01$, with reliable regional differences also obtained, $F(5,255) = 8.4$, $p < .001$. No group $\times$ region interaction was found ($p > .10$). P3a latency was assessed with the same MANCOVA, but no

Table 2. Mean and SD of P3a Amplitudes (μV) at Three Midline (Fz, Cz, and Pz), Three Left (F3, C3, and P3), and Three Right (F4, C4, and P4) Electrodes for the Alcoholic and Control Group

	Control	Alcoholic
Fz	10.60 (5.79)	9.47 (7.27)
F3	9.20 (5.15)	8.08 (6.42)
F4	9.15 (5.38)	8.23 (6.62)
Cz	14.66 (6.95)	11.68 (6.30)
C3	12.03 (5.65)	10.42 (5.78)
C4	11.75 (6.56)	10.51 (6.87)
Pz	14.66 (6.79)	11.62 (5.89)
P3	12.88 (5.97)	10.22 (5.63)
P4	12.69 (5.79)	10.22 (5.49)

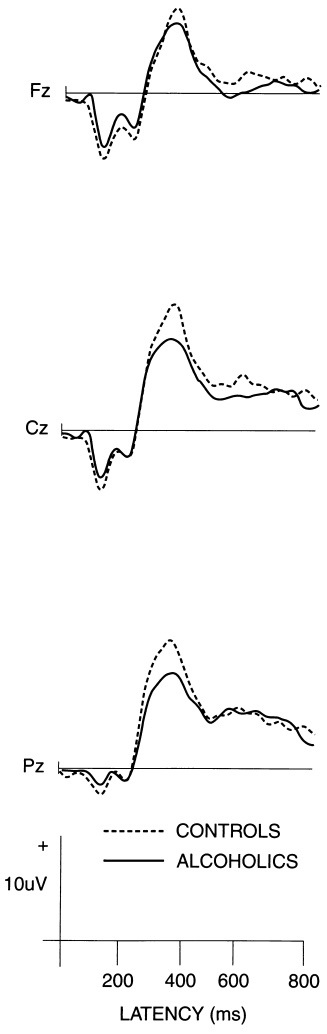

Figure 3. Control and alcoholic subject grand average event-related potentials from nontarget stimuli for the midline electrodes.

significant outcomes were obtained ($p > .40$ in all cases). Thus, the nontarget stimuli elicited different P3a amplitudes for the control compared to alcoholic subjects, although no specific regional differences were observed.

Current Source Density Analysis

Figure 4a and 4b illustrates the CSD maps for the nontarget P3a in both groups. On visual inspection, both groups showed more anterior distributions for the nontarget compared to the target. Control subjects manifested stronger current densities than alcoholics for the nontarget. As can be seen on Figure 4a, there were more sources and sinks in the alcoholics than in the control subjects. CSD maps appeared more organized in control subjects than alcoholics for both targets (P3b) and nontargets (P3a), but appeared most disorganized for the nontarget in alcoholics. For the nontarget, alcoholics demonstrated predominant sources in one portion of right frontal, central, right, left, and mid-parietal, and right occipital areas; sinks occurred in right frontal, left central, and right temporal regions. Control subjects demonstrated predominant sources in the entire central, parietal, and occipital regions; sinks occurred in the right frontal region. For the target, alcoholics demonstrated predominant sources in the parieto-occipital region; sinks occurred in right and left-frontal-central region. Control subjects also demonstrated predominant sources in parieto-occipital region; sinks occurred in right and left frontal-temporal region. On visual inspection, it appears that CSD maps for the target (P3b) were more similar between the two groups than CSD maps for the nontarget (P3a) with this paradigm; however, the results of the bootstrap analysis method (Tables 3 and 4) indicate that the distributions between alcoholics and control subjects were significantly different for both the nontarget and the target in all regions.

Discussion

The present study employed an auditory three-stimulus paradigm to elicit the P3a and P3b components in alcoholic and control subjects. Although the subject groups demonstrated similar distributions of amplitude and latency for the nontarget and target stimuli, P3a amplitudes were smaller overall for the alcoholics compared to control subjects. Different group CSD patterns were also found, which suggests that neuroelectric mechanisms underlying the P3a component were quite different for the two groups. Previous studies, using active processing paradigms, have found substantial group differences only when the discrimination task was difficult (Biggins et al 1995; Rodriguez-Holguín et al 1999; Pfefferbaum et al 1991; Realmuto et al 1993). Because the auditory target/standard discrimination required of the present study elicited reliable group differences for the P3a from the nontarget stimulus (cf. Comerchero and Polich 1998, 1999; Katayama and Polich 1998) it is reasonable to conclude that ERP task difficulty is a critical variable for demonstrating alcoholic versus control P3a effects. Similarly, task difficulty has been found to be an important variable in determining P3b differences in individuals at risk for alcoholism (cf. Polich and Bloom 1999; Polich et al 1994). Furthermore, visual or somatic stimuli have been used to elicit P3a (e.g., Courchesne et al 1975; Yamaguchi and Knight 1991), but the majority of clinical reports have employed auditory stimuli because they are easy to produce, readily capture attention, and have provided much of the basic data about P3a. Thus, this three-tone discrimi-

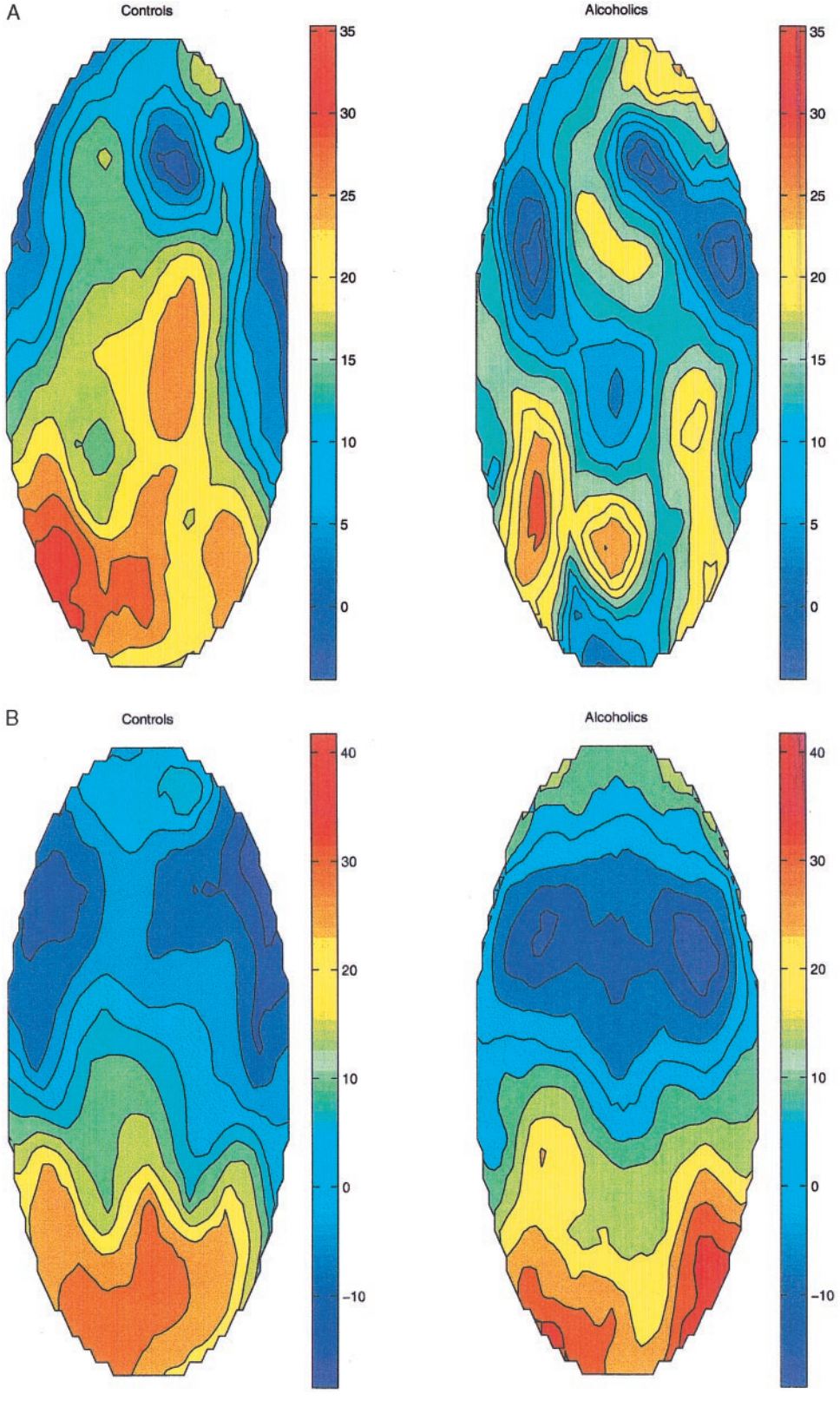

Figure 4. **(A)** Current Source Density maps of P3a from the nontarget stimuli for control and alcoholic subjects (unit: $\mu V/r^2/cm^2$, r = head radius). **(B)** Current Source Density maps of P3a from the target stimuli for control and alcoholic subjects (unit: $\mu V/r^2/cm^2$, r = head radius). Red, target; blue, nontarget; green, standard.

Table 3. Mean *Z* Score Values from the Current Source Density Comparisons for Each Major Electrode Region in Nontarget P3

Region	Alcoholic vs. control subjects	Random-1 vs. random-2	*t* value (df = 398)[a]
Frontal	2.82	2.15	14.6
Central	2.42	1.87	13.7
Parietal	2.60	2.01	14.1
Occipital	2.46	2.01	9.5
Right temporal	2.64	2.03	13.0
Left temporal	2.35	1.82	13.2

See Figure 1 for text and details.
[a]All statistical outcomes obtained $p < .0001$.

nation task provides a useful and reliable clinical device for alcohol study.

P3a, Alcoholism, and Frontal Lobe Dysfunction

Although the precise location of the P3a generator is unknown, the frontal cortex has been implicated, because the response is markedly affected by frontal cortical deficits: Patients with circumscribed lesions of dorsolateral frontal cortex have reduced P3a amplitudes, with relative sparing of P3b (Knight 1984)—a result found for P3a generated in the auditory, visual, and somatosensory modalities (Yamaguchi and Knight 1991). A positron emission tomography (PET) study using a three-tone (novel) auditory discrimination task reported that P3a amplitude was positively correlated with anterior cingulate activity and negatively correlated with temporal activity in normal subjects. Moreover, P3b amplitudes were negatively correlated with posterior cingulate tracer uptake, but positive correlations with P3b amplitudes were found in various frontal and temporal regions (Ebmeier et al 1995). P3a and P3b amplitudes have also been differentially related to frontal and temporal neuroanatomical structure sizes from MRI, because automatic and effortful attention ERP manipulations correlated with frontal and parietal gray matter volumes, respectively (Ford et al 1994).

Neuroimaging studies also support the hypothesis that alcoholics exhibit general cortical and specifically frontal lobe deficits compared to control subjects, perhaps because of excessive alcohol consumption. Computerized tomography imaging has found cortical atrophy in alcoholics and smaller P3b amplitudes than alcoholics without cortical atrophy (Begleiter et al 1980). MRI measures have revealed volume losses in the diencephalon, caudate nucleus, dorsolateral frontal cortex, parietal cortex, and mesial temporal lobe in alcoholics (Jernigan et al 1991). In addition, older alcoholics had less prefrontal gray matter relative to a younger alcoholics, and the cortical white matter volume deficit in the older alcoholics was especially severe in the prefrontal and frontal regions (Pfefferbaum et al 1997). PET measures have found decreased local cerebral metabolic rate for glucose bilaterally in the medial frontal area for alcoholics compared to normal control subjects, with the severity of the clinical neurological impairment significantly correlated with the degree of hypometabolism in the medial frontal region (Gilman et al 1996). Furthermore, the local cerebral metabolic rate for glucose was significantly decreased in a sagittal strip of the medial frontal cortex in alcoholics, with a reliable relationship between glucose metabolic rate in the medial frontal region and Wisconsin Card Sorting Test performance (Adams et al 1993)—a well-established index of prefrontal neuropsychological function (Shimamura 1995). Taken together with ERP studies, it is reasonable to suppose that alcoholics demonstrate considerable dysfunction in frontal cortex and especially prefrontally.

Humans with prefrontal damage are susceptible to proactive interference and perform poorly on neuropsychological tests that require response inhibition (Shimamura 1995; Stuss et al 1982). ERP and other measures suggest increased distractibility and impaired gating of inputs to primary auditory and somatosensory cortex in frontal lobe damaged patients (Knight et al 1989; Woods et al 1986; Yamaguchi et al 1990). Furthermore, animal studies indicate that in addition to inhibition of distractibility, the prefrontal cortex is also important for the early selection of sensory inputs, such that damage to this area results in disinhibition of input to primary cortical regions (Knight et al 1989; Skinner and Yingling 1976; Yamaguchi et al 1990; Yingling et al 1976). In sum, varied evidence suggests that frontal lobe deficits affect information processing efficacy by disengaging the inhibitory mechanisms normally involved in providing a cohesive structure to incoming sensory events—a deficit pattern that is highly consistent with the reduced P3a amplitudes found for alcoholics compared to unaffected controls in the present study.

Additional support for this perspective comes from a comparison of go and no-go ERP paradigms in alcoholics and subjects at high risk for alcoholism, which produced

Table 4. Mean *Z* Score Values from the Current Source Density Comparisons for Each Major Electrode Region in Target P3

Region	Alcoholic vs. control subjects	Random-1 vs. random-2	*t* value (df = 398)[a]
Frontal	2.34	2.64	9.8
Central	2.62	2.32	8.7
Parietal	2.84	2.51	10.0
Occipital	2.64	2.26	8.7
Right temporal	2.92	2.55	10.4
Left temporal	2.60	2.24	10.2

See Figure 1 for text and details.
[a]All statistical outcomes obtained $p < .0001$.

reduced P3b amplitudes in both tasks (Cohen et al 1997a, 1997b), a finding that implies that inhibitory deficits may develop in the thalamus in conjunction with other central structures (Roberts et al 1994). This hypothesis is also consistent with the claim that the positive-going P3 reflects the activation of inhibitory processes (Born et al 1982; Rockstroh et al 1992; Schupp et al 1994; Woodward et al 1991). Thus, alcoholism may be caused at least in part by an increase in CNS hyperexcitability, which results from the decrease in cortical inhibition (Begleiter and Porjesz 1999).

P3a, Alcoholism, and Current Source Density

The most prominent current sources are apparent more anteriorly for the nontarget compared to the target stimulus in both groups. This finding agrees with the previous potential distribution studies (Courchesne et al 1975; Knight 1984). The difference in distribution of CSD maps to the nontarget stimulus between control subjects and alcoholics suggests that alcoholics have disturbances in P3a generation. Although the frontal region is not the sole generator of P3a (Knight 1984; Yamaguchi and Knight 1991) it is the most critical region associated with P3a generation. Given the evidence for comprehensive intercortical connections among sensory-motor and association cortices (Kupferman 1995), damage to one domain underlying P3a generation could readily produce dysfunction in the entire P3a generation network. Because imaging studies have found dysfunction in several brain regions, including the frontal region in alcoholics (Adams et al 1993; Gilman et al 1996; Pfefferbaum et al 1997), the difference in CSD maps may not be solely due to the frontal lobe. It is suggested, however, that the frontal lobe plays an important role in determining the difference in CSD maps between alcoholics and controls.

Taken together, the lower amplitude and weaker sources to rare stimuli coupled with the lack of topographic specificity in the CSD maps of alcoholics compared to control subjects, suggests that alcoholics respond in a disorganized manner, perhaps reflecting an inefficiency in brain functioning. This global pattern of electrophysiological response suggests a lack of differential inhibition in alcoholics, perhaps reflecting underlying CNS hyperexcitability.

Collaborative studies on the Genetics of Alcoholism (H. Begleiter, SUNY HSCB, Principal Investigator, T. Reich, Washington University, Co-Principal Investigator). This collaborative study includes six different centers where data collection takes place. The six sites and Principal Investigator and Co-Investigators are as follows: Indiana University (J. Nurnberger, Jr., T.-K. Li, P.M. Conneally, H. Edenberg); University of Iowa (R. Crowe, S. Kuperman); University of California at San Diego and The Scripps Research Institute (M. Schuckit, F.E. Bloom); University of Connecticut (V. Hesselbrock); State University of New York, Health Sciences Center at Brooklyn (B. Porjesz, H. Begleiter); Washington University in St. Louis (T. Reich, C.R. Cloninger, J. Rice). This national collaborative study is supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) by U.S.P.H.S. grants NIAAA U10AA08401, U10AA08402, and U10AA08403. The superlative assistance of Arthur Stimus, David Chorlian, and Kongming Wang on this project is gratefully acknowledged.

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